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TOPICAL BETA RAY THERAPY FOR SUPERFICIAL SKIN CARCINOMATA AND KERATOSES*

By MERALL ROTH, M.D., *and* JAMES N. CASTLE, A.B.
SAN FRANCISCO, CALIFORNIA

BETA rays from radium plaques have been used successfully for many years for the treatment of superficial lesions. The dosages were recorded by giving the strength of the source, the size, the filtration, and the time of exposure.[12] Therapists relied on their clinical experience to determine the dosage without making physical measurements of the radiation from the plaque and, for the most part, continue to do so even though such measurements were available since 1946 from the work of Blomfield and Spiers,[3] and Neary.[11]

In 1941, Low-Beer[6,7,8] introduced the use of P^{32} on blotting paper. He conducted extensive clinical investigations and with his associates studied the surface doses, the penetration, and the biologic and histologic reactions. He reported visible biologic effects to a depth of 5 mm. Beta rays of P^{32} have a maximum range of 8 mm. in tissue.

Henshaw, Snider, and Riley[4] in 1949 reported the incorporation of red phosphorus in thermosetting plastic and its activation in the uranium pile. In England, in 1952, Sinclair and Blondal[13] reported the use of half millimeter sheets of flexible plastic impregnated with P^{32} by activation in the pile, then cut to desired size for clinical application.

METHODS OF PREPARATION OF BLOTTING PAPER PATCHES

1. *Multiple Droplet Method.* Our method was originally based on Low-Beer's technique. Until December 1953, we applied P^{32} to the blotting paper in a similar fashion, using capillary pipettes instead of a tuberculin syringe. The patches were cut to fit the lesion with at least a 3 mm. border of normal skin. They were measured by tracing on millimeter-ruled graph paper and backed by scotch tape. The solution was distributed drop by drop as evenly as possible behind a beta ray screen of half-inch lucite and then dried under an infrared lamp before application. Our concentration was 167 μc per cm.^{2}, so that a twenty-four hour application gave a dose of 4,000 μc hr./cm.^{2}. Low-Beer's dose is about the same, but the concentration is one-half and the time twice that which we employed.

* From the Radiological and Radioisotope Services, Veterans Administration Hospital, and the Department of Radiology, University of California Medical Center, San Francisco, California.

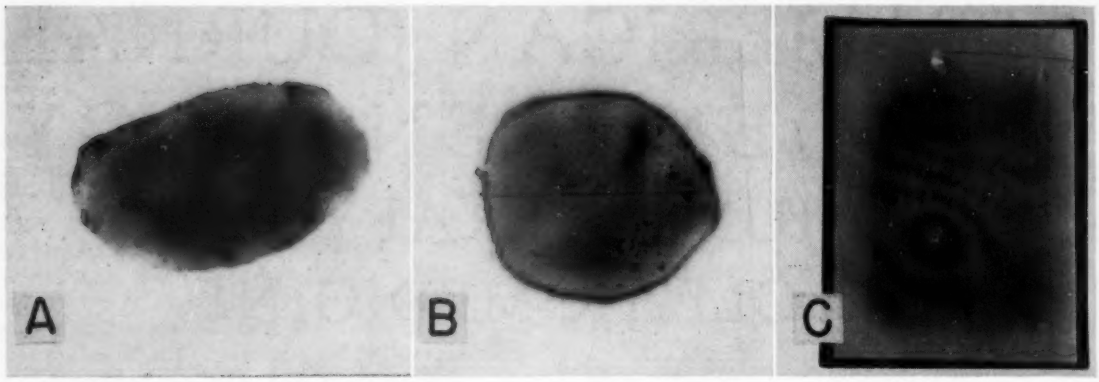

FIG. 1. Autographs of patches, multiple droplet method. The distribution of activity in the patches varies with the position and size of the droplets and the volume of solution applied. The density of the droplets decreases with increased wetting. This spreads the activity through the paper and causes migration of the P^{32} to the edge. There was excessive wetting in Patch *C*. This washed the activity out of the center of the patch. Treatment was successful with Patches *A* and *B*, but failed with *C*.

There were occasional failures. They could be explained in three ways: (a) the lesions were thicker than the effective range of the beta particles; (b) the quantity of P^{32} was inadequate; (c) the distribution of the radioactive solution was poor. The first could be avoided by selecting lesions that did not exceed a millimeter in thickness, the second by checking the activity of the isotope and properly calculating the dosage, and the third by making radioautographs to show the distribution of activity in the patch (Fig. 1).

We made some radioautographs of test patches (Fig. 2). Those that were poorly prepared had a distribution of activity that could account for a failure. Patches made with a single application had a varied pattern. The uniformity depended on the accuracy in spacing the droplets. Poor results occurred more frequently when they were made with two or more applications of a low activity solution. In addition to the problem of getting an adequate distribution, we felt that the method was slow with an exposure hazard to the worker when the patches were large or several of them had to be made.

Since bakelite plaques are rigid and not adaptable for general use and impregnated plastic is not available in this country, we set out to improve the blotting paper

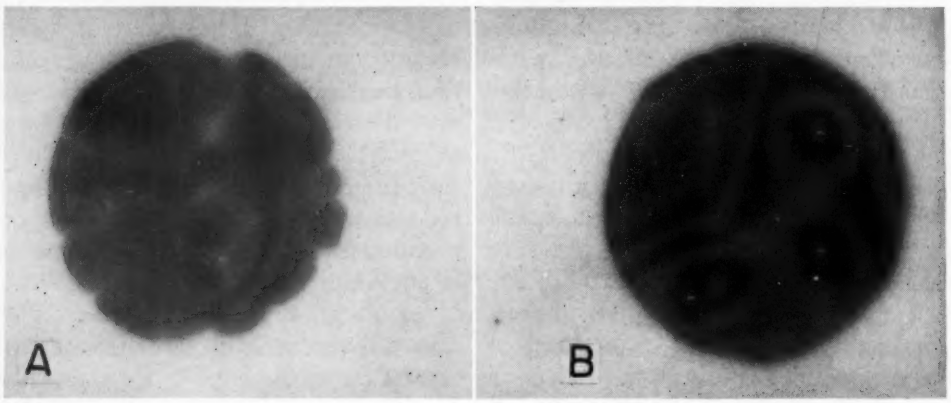

FIG. 2. Autographs of test patches, multiple droplet method. (*A*) Single application. (*B*) Double application. Note the variation in distribution and size of the droplets. The paper was saturated in *B* and migration of the P^{32} to the margin of the patch produced a slight edge effect.

method in a way that would be simple and at the same time provide a reasonably homogeneous distribution of activity.

2. *Edge Immersion of Individual Patches.* This is the first modification of the original method. The patch is cut to fit the lesion and measured in the same way, but no scotch tape backing is used. The volume of water that will saturate a square centimeter of patch is predetermined (0.05 ml. for our paper) and this is multiplied by the area of the patch. The appropriate volume of P^{32} is pipetted and put in a shallow container. The edge of the patch is immersed in the solution (Fig. 3) so that it is taken up by capillarity. If the patch is large, it may be filled from opposite edges. It is then dried thoroughly and the distribution is checked with an autograph.

The activity per square centimeter is calculated by multiplying the concentration of the stock solution by the volume taken up in this area. The lesion is treated to 4,000 μc hr./cm.^{2} The treatment time may range from ten to fifty hours.

Example:

Concentration of stock solution 2 mc/ml.

Uptake by blotting paper patch = 0.05 ml./cm.^{2}

Area of patch = 10 cm.^{2}

$$\frac{2{,}000\ \mu c}{ml.} \times \frac{0.05\ ml.}{cm.^2} = 100\ \mu c/cm.^2$$

$$\frac{4{,}000\ \mu c\ hr.}{cm.^2} \div \frac{100\ \mu c}{cm.^2} = 40\ hr.$$

Volume of P^{32} solution required = 0.05 ml. × 10 = 0.5 ml.

The concentrations of stock solution, varying from 1.6 to 8 mc/ml., will give a range of treatment times from ten to fifty hours. High activities may be diluted to provide a convenient treatment time as twenty-four or forty-eight hours, or to conserve the solution.

Autographs of the patches (Fig. 4) demonstrate an almost homogeneous distribution of activity, with the exception of an increased concentration at the edge due to capillarity and evaporation. Since the solution dries more rapidly at the edge, capillarity carries more activity to it. Usually the edge of immersion has the greatest concentration. The increased activity peripherally causes an indeterminate degree of reduced activity centrally. The loss to the edge is directly related to the ratio of the perimeter to the area and is more for small patches than for large ones. Sometimes fronts are formed. This is due to a transient arrest in the flow of the P^{32} through the blotting paper. Sharp corners particularly have a heavy concentration (Fig. 5), hence they should be rounded off. Beveling the margin of the patch prior to the immersion does not reduce the edge effects appreciably. A double ring of density occurs, the outer one being the greater.

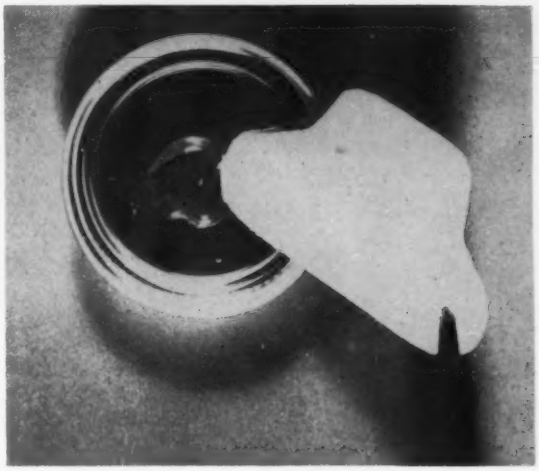

FIG. 3. Preparation of a blotting paper patch by the edge immersion technique. The volume of P^{32} that will saturate the patch is placed in a shallow metal container. This is taken up from an edge by capillarity. The radioactive solution may be diluted if the activity is too high.

3. *Immersion of Large Patches.* Since some patients have several lesions of varying size and shape, we have devised a second modification from which patches are cut as required. The volume of P^{32} solution that would saturate a three-inch square piece of paper (2.9 ml. in 58 cm.^{2} for ours) is placed in a lucite dish of the same size

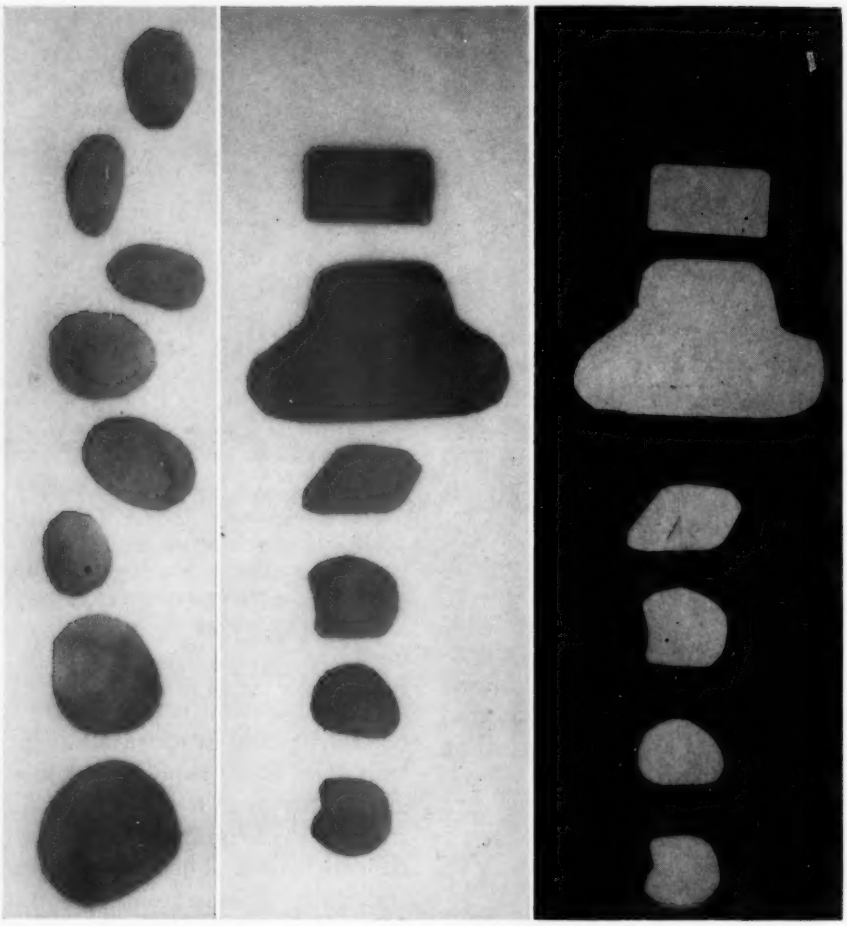

FIG. 4. Case 1. Radioautographs of representative patches prepared by the individual edge immersion technique. The concentration is greater at the leading edges than at the far ones. Some of the patches have a "front" in them. The margins are rounded to avoid concentration at the corners. Patches prior to immersion are also shown.

(Fig. 6*A*). A few milligrams of dibasic sodium phosphate is added as carrier to promote uniform absorption in the paper and to minimize loss of activity to the dish. A trace of wetting agent* is also added to facilitate spreading of the liquid. The blotting paper is then immersed and autographed (Fig. 7). The concentration of the P^{32} may vary from 1 to 5 mc/ml. and the activity of the patch from 50 to 250 μc/cm.^{2}. The treatment time will accordingly range from ten to fifty hours.

The pattern of the lesions is traced on the outside of a folded piece of 0.01 inch lead foil cut to fit the blotting paper square. An inner surface is covered with glue and the patch is inserted into it (Fig. 6*B*). The patterns are then cut (Fig. 6*C*), the loose foil is discarded and the blotting paper with foil backing is applied to the lesion, molded and then fixed with adhesive tape. Since our lead foil provides about 60 per cent backscatter, the dose is reduced from 4,000 to 2,500 μc hr./cm.^{2}. The treatment time is governed by the activity of the patch. There is about 5 per cent transmission through our lead. This reduces the exposure hazard markedly and permits safe handling by the trained worker.

* Sodium heptadecyl sulfate, Tergitol #7, Carbide & Carbon Chemical Company.

REPORT OF CASES

Case 1. F.C., a sixty-seven year old white male, was admitted to this hospital for the third time on January 4, 1954, for treatment of multiple superficial skin cancers and hyperkeratoses of the face and neck. The lesions itched and burned. Several biopsies were taken. All showed squamous cell carcinoma. The Tumor Board recommended that the superficial malignant lesions, as well as some of the keratotic ones be irradiated, the method to be determined by the radiologist.

Past History. The patient had been a ranch hand in Idaho since the age of fourteen. He had had dark-auburn hair in earlier years. He freckled easily on exposure to the sun and burned readily but never tanned. Keratotic lesions of the face and neck had been present for the past twenty to twenty-five years, untreated until 1946. Since then, a number of lesions had been treated by either surgery or irradiation with resultant scarring. Scars about the eyes produced a bilateral ectropion. A large defect on the right side of the face was due to an infiltrating recurrent squamous cell carcinoma, which had been ultimately controlled by surgery and a radium mold.

Physical Examination. Besides the numerous scars, the face and neck were covered with many superficial scaly keratotic lesions. Several keratoses were also present on the backs of the hands. Otherwise, the examination was not remarkable.

Course of Therapy. The lesions were so numerous that the treatment had to be given at intervals. P^{32} patch therapy was supplemented by low voltage roentgen irradiation for some of the small lesions.

First Group (Fig. 4 and 8). Nine air-backed patches prepared by the edge immersion technique for individual patches were applied to the face for twenty-four hours on February 18, 1954. They varied in size from 2.2 to 33 cm.^{2} (Fig. 8*A*). The observations were made from the end of application. *Four days*. This was the first observation. Erythema was present at all of the treated areas. *Eleven days*. The reactions increased to a moderate erythema and some crusting. *Seventeen days* (Fig. 8*B*). The acme of the reactions was reached. The erythema was severe and the crusting was heavy. *Four weeks* (Fig. 8*C*). The irradiated lesions were definitely smaller with healing advancing from the margins. *Eight weeks*. Almost all evidence of the lesions had disappeared. No biologic effect was observed to correspond with the increased concentration of P^{32} at the edge of the patches. *Nine weeks* (Fig. 8*D*). The hair had regrown in the bearded areas indicating that the radiation effects were not sufficiently deep to destroy the hair follicles. *Four months*.

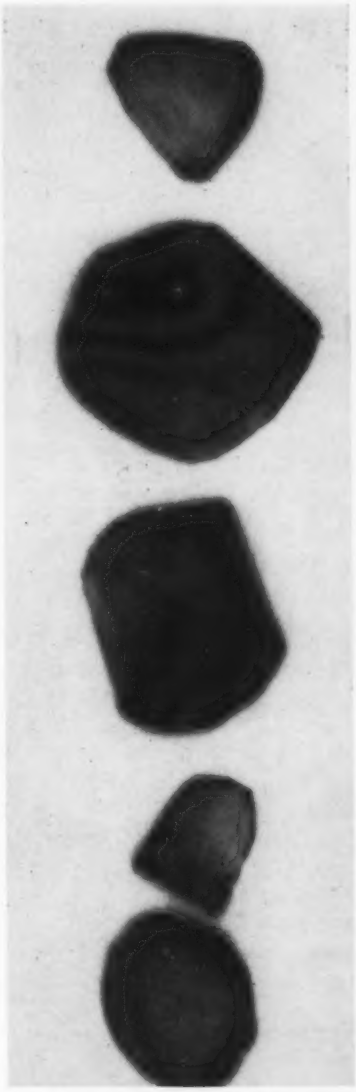

Fig. 5. Radioautographs of blotting paper patches prepared by the individual edge immersion technique for one of the patients who had been studied. Note the edge effect with a greater concentration at the leading edge. A particularly heavy concentration is present at some of the sharp corners. Beveling at the edge has not reduced the edge effect. It only produced an inner ring of lower density.

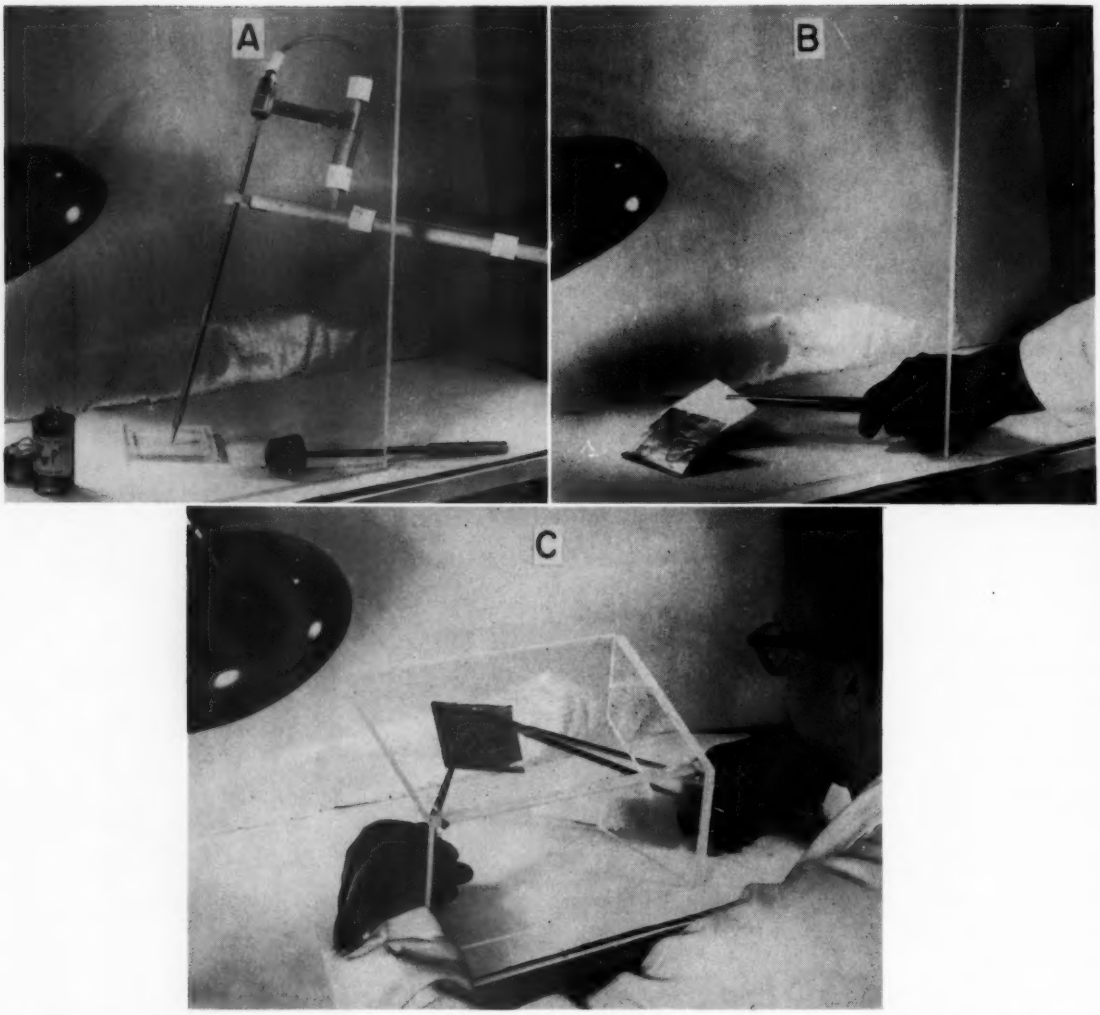

FIG. 6. Preparation of a 3 inch square patch by the immersion technique. (*A*) Delivery of a fixed quantity of P^{32} sufficient to saturate the patch into a lucite dish of the same size by means of a remote pipette. Carrier and wetting agent are then added and the patch is immersed and dried. (*B*) The patterns are traced on the outside of a folded lead foil. An inner surface is covered with glue and the patch is inserted. (*C*) The patterns are cut and the loose foil is discarded. Note the protection provided by the lucite shields.

Four of the lesions had a normal appearance and five showed a mild pink atrophy. *Fifteen months.* A mild superficial white atrophy of all lesions had appeared. The beard growth persisted.

The patient also received superficial roentgen irradiation (half-value layer 0.57 mm. Al, target skin distance 20 cm.) to five small keratotic lesions of the face and neck between February 23 and March 4, 1954. The therapy scheduled varied between a single session of 2,000 r in air to 5,000 r in air, fractionated over a ten day period. All of the lesions ultimately healed with mild white scarring and permanent epilation of bearded areas. No appreciable difference was observed between the single and fractionated therapy.

Second Group (Fig. 4 and 9). Fifteen lesions of the face and neck were treated for forty-eight hours by patches prepared in the same way as for the first group. Seven were applied on April 26, 1954, and eight were applied three days later. They varied from 2 to 24 $cm.^2$ in size. Most of the first series of seven were applied to the face, and nearly all of the second series were applied to the neck (Fig. 9*A*).

First Series. *One day* (Fig. 9*B*). The initial observation after removal of the patches showed

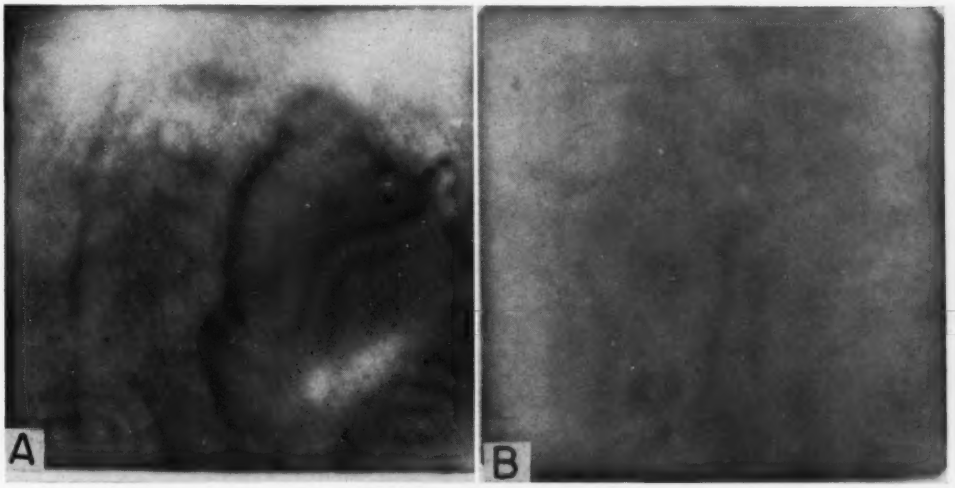

Fig. 7. Radioautographs of 3 inch square patches. (*A*) No carrier or wetting agent added to the radioactive solution. Note the irregular fronts and uneven distribution. (*B*) Dibasic sodium phosphate (Na_2HPO_4) added as carrier and Tergitol #7 as wetting agent. The distribution is nearly homogeneous except for the edge effect.

a brisk erythema of all lesions. *Three days*. The patient reported that tiny vesicles formed on most of the lesions. *Eight days* (Fig. 9*C*). The vesicles broke, the serum coagulated, and crusts began to form. *Eleven days*. Itching and burning were severe, requiring sedation. *Fifteen days* (Fig. 9*D*). The acme was reached. The erythema was severe and the crusts were heavy.

Second Series. *One week* (Fig. 9*C*). This was the first observation after the patches were removed. Most of the reactions were mild. Some showed fine crusts and scales. *Two weeks* (Fig. 9*D*). The acme was reached. The erythema was moderately severe and the crusts were moderately thick.

Both Series. *Three weeks* (Fig. 9*E*). The reactions were subsiding. The crusts had fallen from most of the lesions, and they were covered by a thin pseudomembrane. The beard was sparse. Itching and burning had lessened. *Four weeks* (Fig. 9*F*). The crusts had reformed but they were smaller. The erythema was minimal to moderate. Healing was in progress and itching and burning had ceased. *Five weeks* (Fig. 9*G*). Healing was almost complete. Only a few crusts persisted. *Seven weeks* (Fig. 9*H*). Healing was complete except for one very small central crust. Most areas were pale pink and appeared mildly atrophic. The beard had almost completely regrown. *Thirteen months*. The lesions showed depigmentation or mild white atrophy. The beard persisted.

Third Group. The patient returned for a fourth admission during May, 1955, because of recurrent infiltrating squamous cell carcinoma along the margins of an old graft in the left infratemporal region. This could not be controlled by roentgen irradiation and a program of chemosurgery was instituted. The outcome was doubtful since the lesion had advanced into the outer margin of the left orbit and into the external auditory meatus.* Five new lesions appeared on the face, suspicious for superficial carcinoma. Patches ranging from 3.2 to 38 $cm.^2$ were applied on June 17 for 42.5 hours. They were cut from blotting paper squares that had been prepared by the immersion technique and backed with lead foil. The largest patch was applied to the right upper eyelid. The eyelid had an estimated thickness of 2 to 3 mm. As a precaution, a lucite contact lens was placed against the globe with a nonmetallic anesthetic ointment in the corneal pocket. Its thickness was about 1 mm. peripherally and 1.5 mm. centrally. The eyelids were sutured together and then the patch was applied. Some chemosis was present when the patch and contact lens were removed. This subsided before the acme occurred. Three of the lesions showed a mild erythema on removal of the patch, the other two had a similar reaction on the next day. The acme occurred on the sixteenth and seventeenth days. The erythema was severe but the

* The patient died of general debility in December. The chemosurgeon was unable to remove all of the tumor.

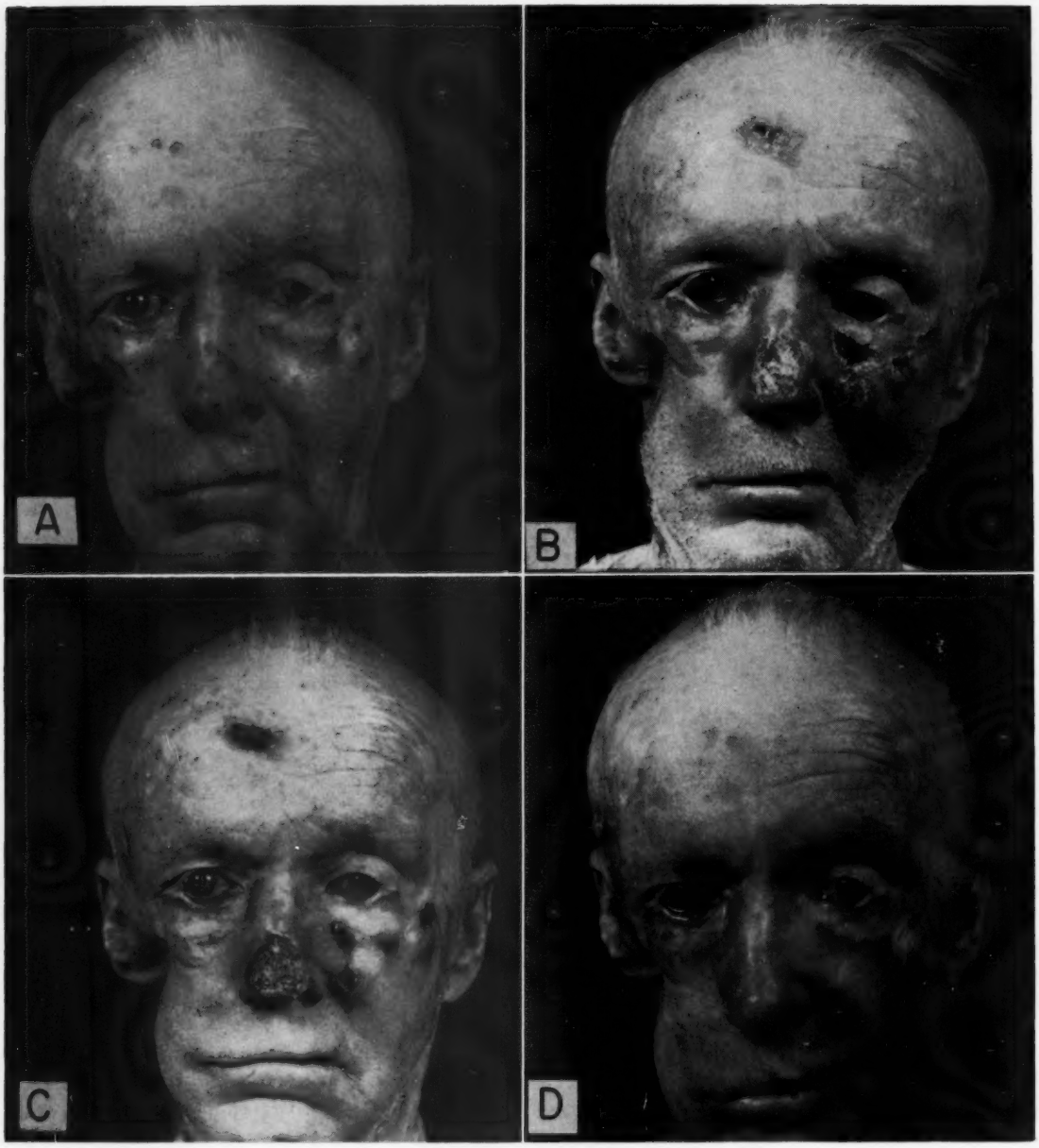

FIG. 8. Case I. Group I Lesions. Air-backed patches, individually immersed, 2.2 to 33 cm.^{2}. Group I lesions visible in the anterior view. (*A*) Prior to patch therapy. (*B*) Seventeen days. The acute reaction is at its acme. The crusting is heavy. (*C*) Four weeks. The crusts are smaller. Healing is beginning at the margins. (*D*) Nine weeks. The healing is complete.

crusting was mild. The eyelashes and eyebrow had epilated. The patient was not seen for nine weeks (three months after removal of the patches). The eyelashes and eyebrows had fully regrown. The eyelid had a slight pink atrophy. Two of the lesions had a mild white atrophy, and two were slightly red and scaly.

CASE II. C.H., an eighty-one year old retired construction worker, presented himself on March 1, 1955, for treatment of multiple pigmented skin keratoses and a small nodular lesion of the left upper eyelid. Biopsy of the eyelid revealed a basal cell carcinoma. The keratoses were so numerous that only seven of

the more suspicious ones were selected for P^{32} treatment. They were on the dorsum of the hands, the left lower forearm and wrist, the nose, and the posterior right ear. Biopsies were taken from three of them. They showed a superficial squamous cell carcinoma for one (right ear) and hyperkeratosis with cellular atypism for two (hands).

Past History. The patient had dark brown hair in earlier years, but had a photosensitive skin. During the past eight to ten years he developed multiple keratoses, some of which were removed surgically.

Physical Examination. This revealed a senile white male with large numbers of pigmented keratoses of the face, nose, ears, trunk and upper extremities. A small biopsy scar was noted in an indurated lesion of the left upper lid. Superficial lesions were present at the inner canthus of the right eye which were suspected of malignant changes.

Course of Therapy (Fig. 10 and 11). Lead-backed patches cut from blotting paper squares prepared by the immersion technique were applied to five of the selected lesions (hands, left forearm and wrist) for twenty-six and one quarter hours on March 2 (Fig. 10*A*), and to two lesions (nose and right ear) for twenty-seven and one-half hours on March 3, 1955 (Fig. 11*A*). They varied in size from 3 to 31 $cm.^2$. Observation times date from removal of the respective patches.

Initial Observation. All lesions had a mild erythema when the patches were removed. *Two days*. The reactions of the nose and ear progressed to a moderate erythema. *Seven days*. The nose and ear showed a moderately severe erythema and a few crusts. *Eleven days*. The reactions progressed for all of the lesions. The erythema was moderate on the forearm, wrist and hands. Some of the lesions began to itch and burn. *Seventeen days* (Fig. 11*B*). The acme was reached for the nose and ear. The reactions were severe with a moderate edema. A thin yellow crust formed beneath which some blood had oozed. *Eighteen days*. This was the acme for the lesions of the forearm, wrist and hands. It was manifested by moderate erythema and bullous epidermolysis. The reactions on the nose and ear decreased slightly. *Nineteen days*. The bullae on the forearm, wrist and hands had sloughed, leaving a moist yellow exudate on the surface. The reactions were a little less. *Three weeks*. The moisture was still present on the forearm, wrist and hands. The erythema was receding but the crusts were a little thicker on the nose and ear. *Four weeks* (Fig. 10*B* and 11*C*). All of the lesions were healing from the margins. There were thin crusts on the forearm, wrist and hands but no erythema. The receding yellow crusts over the nose and ear were thin with patches of dried blood beneath. The edema had subsided. *Five weeks* (Fig. 10*C* and 11*D*). Healing from the margins of all the lesions continued. Those on the forearm and hands had thin, dark-yellow crusts in the center. *Seven weeks* (Fig. 11*E*). The lesions on the forearm, wrist and hands had healed but the epilated hair had not returned. The crusts on the nose and ear were small. *Ten weeks* (Fig. 10*D* and 11*F*). All of the lesions had healed with little or no atrophy. *Three months*. The new skin on the forearm and hands was slightly depigmented, and there was a mild pale pink atrophy of the nose and ear. *Six months*. No changes were noted. *Ten months*. The nose and ear showed a mild white atrophy and the depigmentation of the hands and forearm had increased. *Fifteen months* (Fig. 10E). The depigmentation had progressed. The hair was still epilated.

During the same period the patient also received a skin dose of 5,650 r in thirty-five days to the left eyelid using 250 kv. roentgen rays at 50 cm. target skin distance, half-value layer of 0.57 mm. Cu, and a dose of 4,950 r in twenty-nine days to the skin of the right inner canthus, also with 250 kv. at 50 cm. target skin distance, but with a half-value layer of 1.7 mm. Cu. Reactions in general resembled those on the nose and ear. One month after therapy was completed, the lesions healed with minimal atrophy. The eyebrows and eyelids in the treatment fields had epilated. The eyes were protected by lead shields beneath the lids during the therapy. A follow-up after fifteen months revealed permanent epilation of the eyebrows and eyelashes. The palpebral fissure was narrowed and the margins of the eyelids were thickened.

Case III. J.C., a forty-seven year old white male outdoor worker, presented himself on January 1, 1955, for treatment of eczematoid and keratotic lesions on the dorsum of the hands and on the lower left forearm. An excisional biopsy of one of them revealed a superficial squamous cell carcinoma. Biopsy of two

FIG. 9. Case 1. Group 2 Lesions. Air-backed patches, individually immersed, 2 to 24 cm.^{2}. Group 2 lesions visible in the left lateral view. (*A*) Prior to patch therapy. (*B*) One day. The erythema is brisk. The circled neck lesions have not yet been treated. (*C*) One week. A crust is forming on the face. The neck lesions have a mild reaction. (*D*) Two weeks. The acme is reached. The reaction is severe on the face and the crust is heavy. The effect on the neck lesions is less.

Fig. 9. Case 1. Group 2 Lesions. (*E*) Three weeks. The reactions are subsiding. The crusts have disappeared and lesions are covered by a pseudomembrane formed from a dried thin layer of exudate. The beard is sparse. (*F*) Four weeks. Crusts have reformed but they are smaller. The erythema is minimal to moderate. (*G*) Five weeks. Healing is almost complete. (*H*) Seven weeks. Healing is complete. The beard has regrown.

others showed keratosis with atypical hyperplasia.

Past History. The patient was a former Army engineer. The back of the hands began to itch and burn while he worked in the coral reefs during dredging operations at Midway in 1940, but nothing was observed until after he returned to the States in July, 1941. The skin became dry, red, and scaly. Changes were slowly progressive, and did not respond to topical medication. Sun tolerance was poor.

Physical Examination. This revealed a well developed, red-headed, freckled male with fair skin, appearing his stated age. The dorsum of the hands was dry, red, and scaly. The scar of an excisional biopsy was present on the dorsum of the right hand. A number of crusted and keratotic lesions were present. Some of them were heavily cornified. A large crusted keratotic lesion was located on the dorsum of the lower left forearm.

Course of Therapy (Fig. 12). Six patches varying from 2.8 to 12.7 cm.^{2} in size were applied to selected lesions on the left forearm (Fig. 12*A*) and both hands on January 28, 1955, for thirteen hours and twenty-four minutes. They were cut from blotting paper squares that had been prepared by the immersion technique and backed by lead foil. The observations are as follows: *Two days*. This was the first time that lesions were seen after the patches were removed. Two of them exhibited mild erythema. *Four days*. All of the lesions now had a mild reaction. *Nine days* (Fig. 12*B*). Two of the lesions had a moderate reaction; the others still showed mild changes. *Twelve days*. The lesion

FIG. 10. Case 11. Lead-backed patches, 3 to 17.5 cm.^{2}. (*A*) Prior to patch therapy. (*B*) Four weeks. The bullous epidermolysis which occurred at the acme has subsided leaving a dried crust.

Fig. 10. Case 11. (*C*) Five weeks. Healing is progressive. (*D*) Ten weeks. Healing is complete. The new skin is normal, except for slight depigmentation. (*E*) Fifteen months. The depigmentation has progressed.

FIG. 11. Case 11. Lead-backed patches. Nose 31 cm.^{2}. Ear 23.5 cm.^{2}. (*A*) Prior to patch therapy and roentgen irradiation of left lid and right inner canthus. (*B*) Seventeen days. Acme. The reaction is severe with a moderate edema. Blood oozed beneath the thin crust, especially on the nose. Roentgen therapy is in progress. (*C*) Four weeks. The acute reactions are fading and marginal healing is in progress at the nose and ear. The edema has subsided.

FIG. 11. Case II. (*D*) Five weeks. Healing from the margins of the P^{32} treated lesions continues. Roentgen irradiation to the left lid is completed. The reaction is at its peak. Roentgen therapy to the right inner canthus is almost completed. Note the epilation of eyelashes and eyebrows. (*E*) Seven weeks. Healing of nose and ear is almost complete. The reaction at the right inner canthus is at its peak. (Therapy was completed eleven days before.) The left lid is healing from the margins. (*F*) Ten weeks. Except for a small crust at the right inner canthus, all lesions have healed. A follow-up fifteen months later revealed a permanent epilation of the eyebrows and eyelashes. There was also thickening of the margins of the eyelids and narrowing of the palpebral fissure due to irradiation.

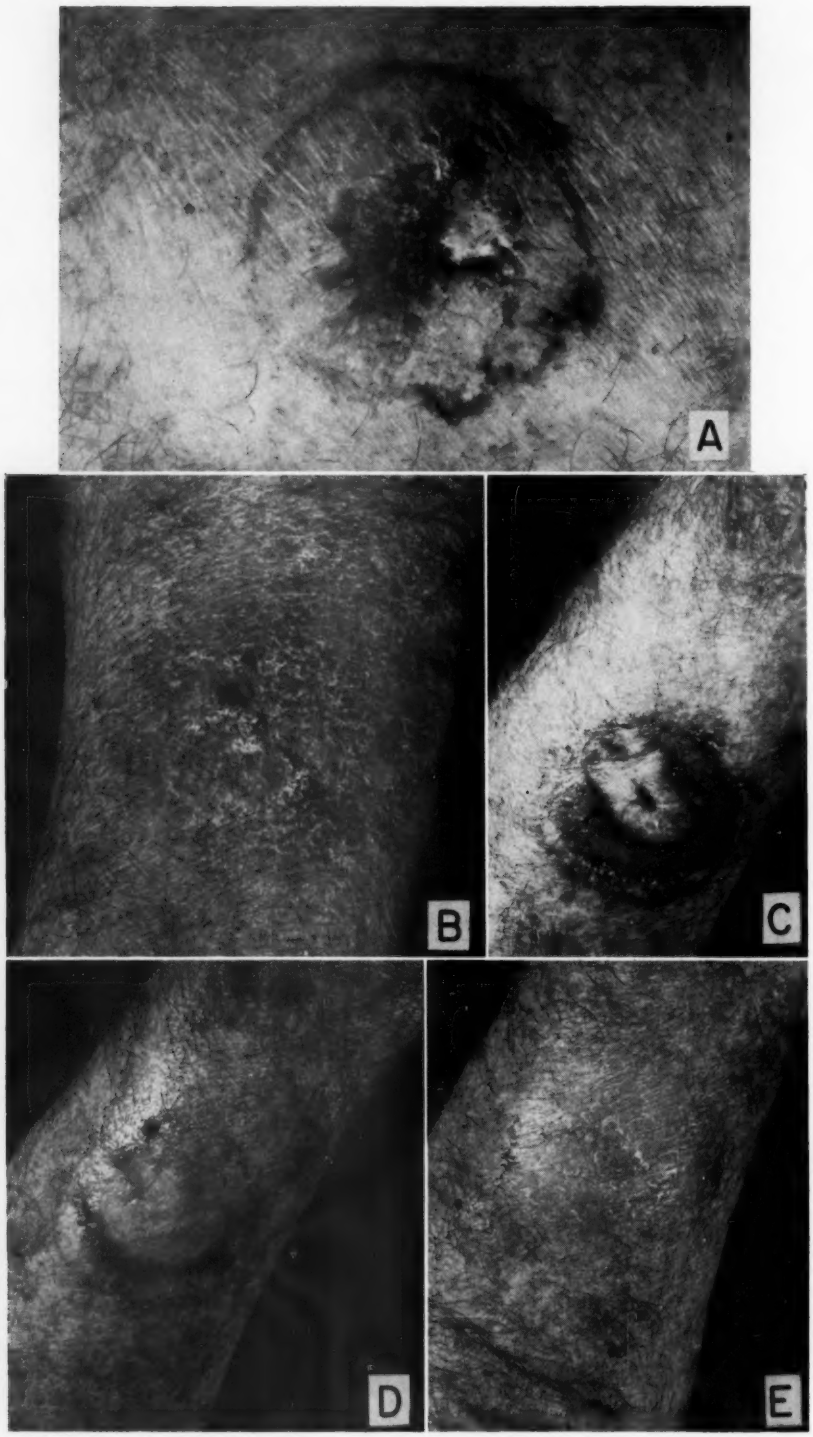

FIG. 12. Case III. Lead-backed patch, 12 cm.^{2}. (*A*) Left forearm prior to patch therapy. (*B*) Nine days. The erythema is moderate. (*C*) Eighteen days. Acme. Severe moist epidermolysis and keratolysis. (*D*) Three weeks. The reaction is subsiding and the cornification has sloughed. (*E*) Five weeks. Healing is almost complete. The hair is epilated.

on the left forearm and one on the dorsum of the left hand became infected. This was complicated by lymphangitis and axillary lymph adenitis. There was response within a week to antibiotics and supportive measures. *Eighteen days* (Fig. 12*C*). The maximal reactions were evident. Four lesions developed a moist epidermolysis and keratolysis of the cornified portions. Two lesions had a slight reaction with some crusting. *Three weeks* (Fig. 12*D*). Regression of the reactions was definite. The cornifications which had undergone keratolysis had sloughed away. *Five weeks* (Fig. 12*E*). The erythema had faded and most of the crusts and scales had fallen off. The hair had epilated.

On March 2, 1955, two additional small patches prepared in the same way were applied to two keratotic lesions on the dorsum of the left hand. The treatment time was twenty-six hours, twelve minutes. A slight erythema was present when the patches were removed. The patient did not return for follow-up until May 3, 1956. At that time all of the treated lesions showed normal but depigmented skin, except the left forearm where mild pale pink atrophy occurred.

Case IV. M.L., a sixty-one year old retired Army colonel, presented himself on December 1, 1954, for treatment of five erythematous scaly skin lesions located on the right breast, left lumbar region, the posterior midthorax, the right groin, and left lower quadrant of the abdomen. The left lumbar lesion was partially removed by curettement at another hospital. Biopsies taken from four of the lesions were diagnosed as superficial basal cell carcinoma.

Past History. The patient stated that when he was in the Philippines in 1944 he was scratched on the right breast, abdomen and back by decaying palm fronds. The lesions recurrently healed and broke down, becoming dry and scaly, then moist. In 1947, they were diagnosed as fungus infections. Since September 1954, there were intermittent itching, oozing of blood, and weeping of yellow exudate, with interval drying and scaling. They did not respond to antifungus therapy. Tolerance to the

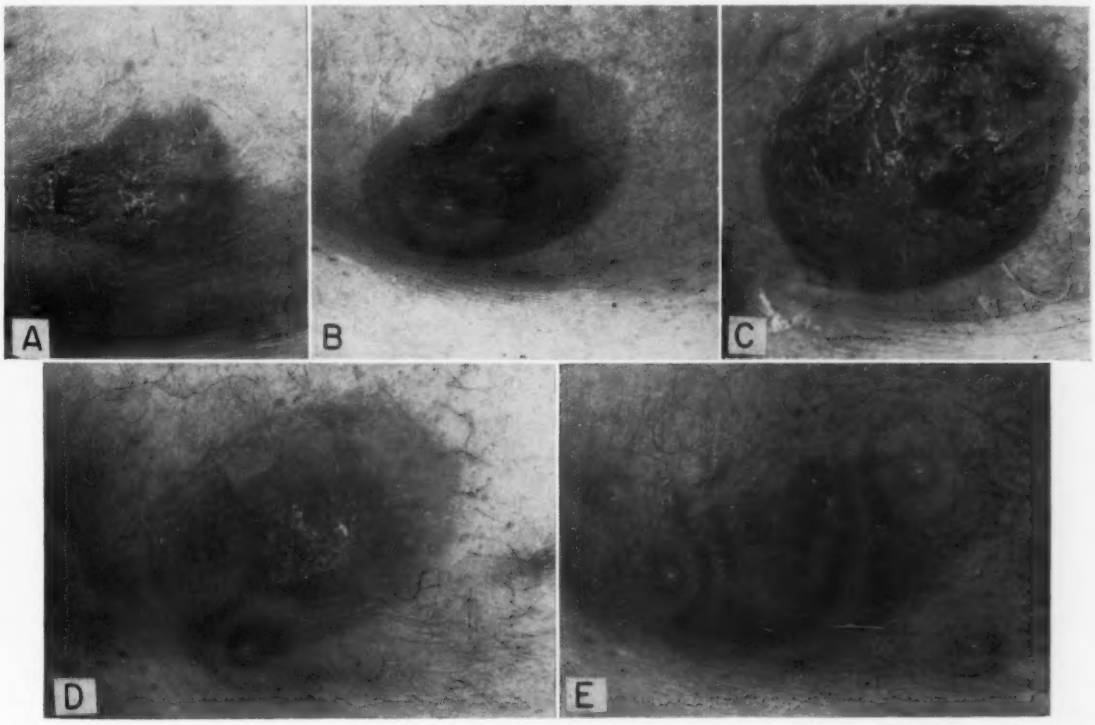

Fig. 13. Case IV. Lead-backed patch, 23.5 cm.^{2}. (*A*) Right nipple prior to patch therapy. (*B*) Three days. There is a brisk erythema and moist desquamation. (*C*) Eighteen days. Acme. The reaction is severe and moist with thin hemorrhagic crusts. A pigmented ring is forming. (*D*) Six weeks. Healing is in progress. Fine scales are present in the central area. The ring of pigmentation is quite distinct. (*E*) Ten weeks. Healing is still not complete. The pigmented ring persists.

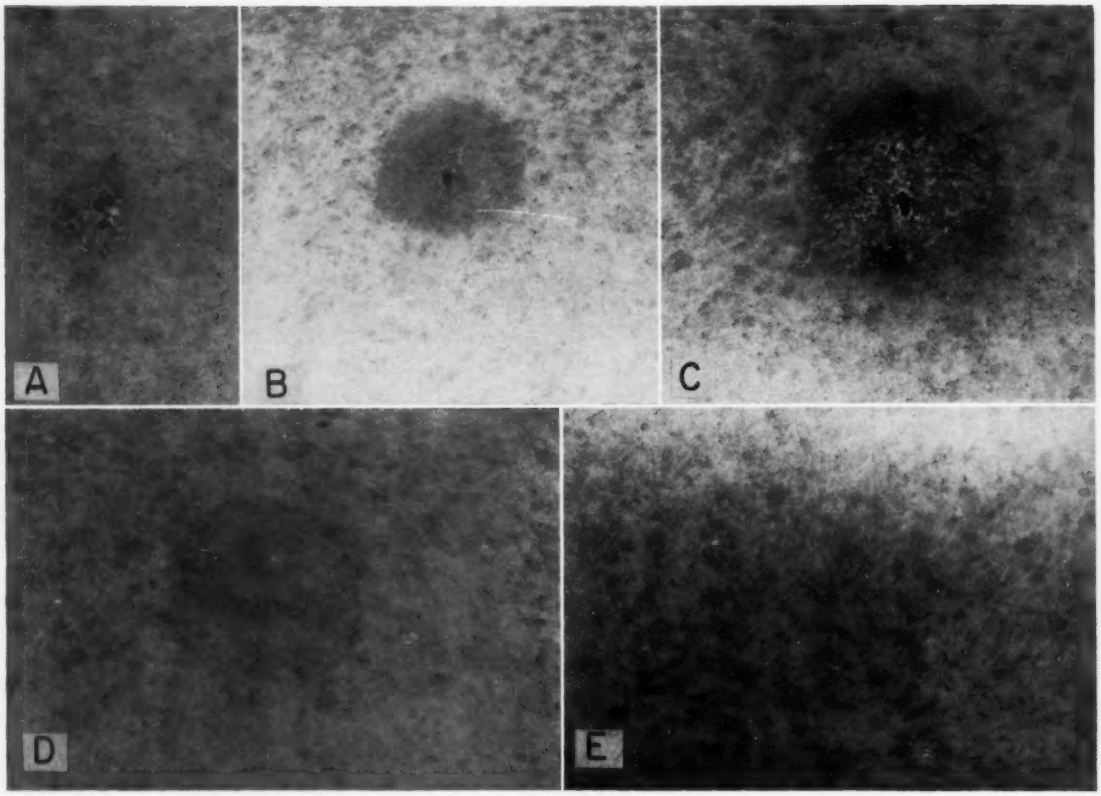

FIG. 14. Case IV. Lead-backed patch, 6.5 cm.^{2}. (*A*) Posterior midthorax prior to patch therapy. (*B*) Three days. Brisk erythema. (*C*) Eighteen days. Acme. The reaction is moderate with thin crusts. (*D*) Six weeks. Healing is in progress and the erythema is subsiding. Freckles are again visible. Note the pigmented ring. (*E*) Ten weeks. Healing is complete. The pigmented ring has faded.

sun was moderate. He had had light brown hair.

Physical Examination. This revealed a healthy, large, well developed, obese male with a ruddy complexion. The skin lesions described above were all erythematous, flat and scaly. Part of the left lumbar lesion was covered by a superficial atrophic scar due to curettement.

Course of Therapy (Fig. 13 and 14). Lead-backed patches cut from blotting paper squares prepared by the immersion technique were applied to four of the lesions described above for forty-nine hours on December 29, 1954. They varied in size from 6.5 to 28.5 cm.^{2}.

Initial Observation. All of the lesions had a brisk erythema on removal of the patches. *Three days* (Fig. 13*B* and 14*B*). The erythema had intensified. There were moist desquamation and some itching of the lesion on the right nipple. *Ten days.* Blood was oozing from the incompletely healed biopsy site at the right nipple. The reactions continued to increase and thin crusts were forming on the lesions. *Eighteen days* (Fig. 13*C* and 14*C*). The acme was reached. Hemorrhagic crusts were present at the right nipple and groin. The lesion in the groin was indurated by inflammation due to the irradiation. Three of the lesions had a severe moist reaction. The fourth, on the back of the thorax, had a moderate reaction and moderate crusting. *Twenty days.* The recovery phase began. The moist reactions were subsiding and pigmentation rings were forming. *Four weeks.* Epithelization was beginning as the reaction subsided. The crusts were thin. The inflammation in the groin receded. *Six weeks* (Fig. 13*D* and 14*D*). The acute reactions had completely subsided. Fine scales were present at the nipple and lumbar lesions. All of the lesions were tanned and had a ring of pigmentation. *Ten weeks* (Fig. 13*E* and 14*E*). The thoracic lesion had healed and was nearly normal in appearance. The tanning and ring of pigmentation had faded. The other lesions still

showed a pronounced pigmented ring but less tanning. There was a slight red atrophy and slight scaling at the nipple. A mild superficial depressed red scar was present in the center of the lesion at the groin. *Five months*. The pigmented rings and tanning had not completely faded from three of the lesions. All of them showed a mild pink atrophy except for the superficial depressed red scar at the groin.

A fifth lesion located on the left lower quadrant of the abdomen was treated with superficial roentgen irradiation (half-value layer 0.57 mm. Al, target-skin distance 20 cm.). A single dose of 2,000 r was given through a 2.5 cm. cone on January 3, 1955. A minimal erythema was observed at the end of the week, with only slight progress by the end of the second week, but at the end of three weeks the peak reaction occurred. It was manifested by a brisk erythema and moist epidermolysis. Thereafter, the reaction subsided, with crusting and healing from the margins. At the end of the tenth week, there was a small central red superficial scar surrounded by tanning and a peripheral ring of pigmentation. By the fifth month, there was partial fading of the tanning and of the pigmented ring. A mild atrophy developed about the scar.

Case v. T.M., a sixty-seven year old male, presented himself for treatment of a small lesion near the end of the nose on November 1, 1954. It began as a scaly, slightly elevated lesion about three or four months before. Later, it became thick and warty. An incomplete excisional biopsy had been done at this hospital on November 7. The diagnosis was senile keratosis with cellular atypism.

Past History. The patient had no unusual exposure to the sun since his retirement ten years ago. Before that he had considerable exposure as an outdoor worker. He stated that he tanned easily without burning, and that he had dark-brown hair in earlier years. Ten years before, a small crusted lesion had been removed by electrocautery from the middle of the bridge of the nose.

Physical Examination. This revealed a small biopsy scar near the end of the nose and a small superficial scar above it. There was nothing else of interest.

Course of Therapy (Fig. 15). A P^{32} patch measuring 25 cm.^{2} was applied to the entire nose as prophylaxis against extension. It was cut from a blotting paper square that had been prepared by the immersion technique and backed with lead foil. It was applied on December 1, 1954, for eleven hours and twelve minutes.

Initial Observation. Slight erythema was present on removal of the patch. *Three days*. The reaction progressed to a moderate erythema, and burning and itching began. *Five days*. Fine scales appeared. *Eleven days* (Fig. 15*A*). The erythema became moderately severe. The nose was moderately edematous, and it was covered by a thin scale. *Sixteen days*. This was the acme of the reaction. The erythema was severe. Moderately thick yellow crusts had formed. Itching and burning also were severe. *Eighteen days* (Fig. 15*B*). The reaction began to recede. *Four weeks* (Fig. 15*C*). Considerable healing occurred at the margins, particularly over the cartilaginous portion of the nose. The crust was now a thin yellow fibrinous pseudomembrane. There was less itching. *Five weeks* (Fig. 15*D*). The crust was thicker but smaller. The erythema had subsided. *Seven weeks* (Fig. 15*E*). Healing was not yet complete. A small crust and some fine scales were still present. *Ten weeks* (Fig. 15*F*). Healing was complete with only slight residual scaling. Except for slight depigmentation, the new skin had a normal appearance. *Three months*. The midportion of the nose had a mild pink atrophy. *Nine months*. A mild white atrophy of the skin had appeared. *Seventeen months*. The white atrophy had progressed slightly.

Case vi. T.P., an eighty-four year old retired mail clerk, returned for a follow-up visit in June, 1955. Large, thickened, keratotic lesions were in front of each ear and left upper lateral neck. Two of the lesions were biopsied and diagnosed as basisquamous cell carcinoma.

Past History. The patient had been treated for several superficial skin cancers of the face. A number of keratoses had appeared during the past several years.

Physical Examination. The skin of the face showed marked senile changes and there were scars of previous irradiation. In addition to the thickened keratoses described above, there were several others which were not thickened and did not show clinical evidence of malignant change.

Course of Therapy (Fig. 16). Four lead foil-backed patches cut from blotting paper squares immersed in P^{32} were applied on June 29, 1955, for twenty-four and one-half hours. The sizes were from 5.5 to 43.6 cm.^{2} (Fig. 16*A*).

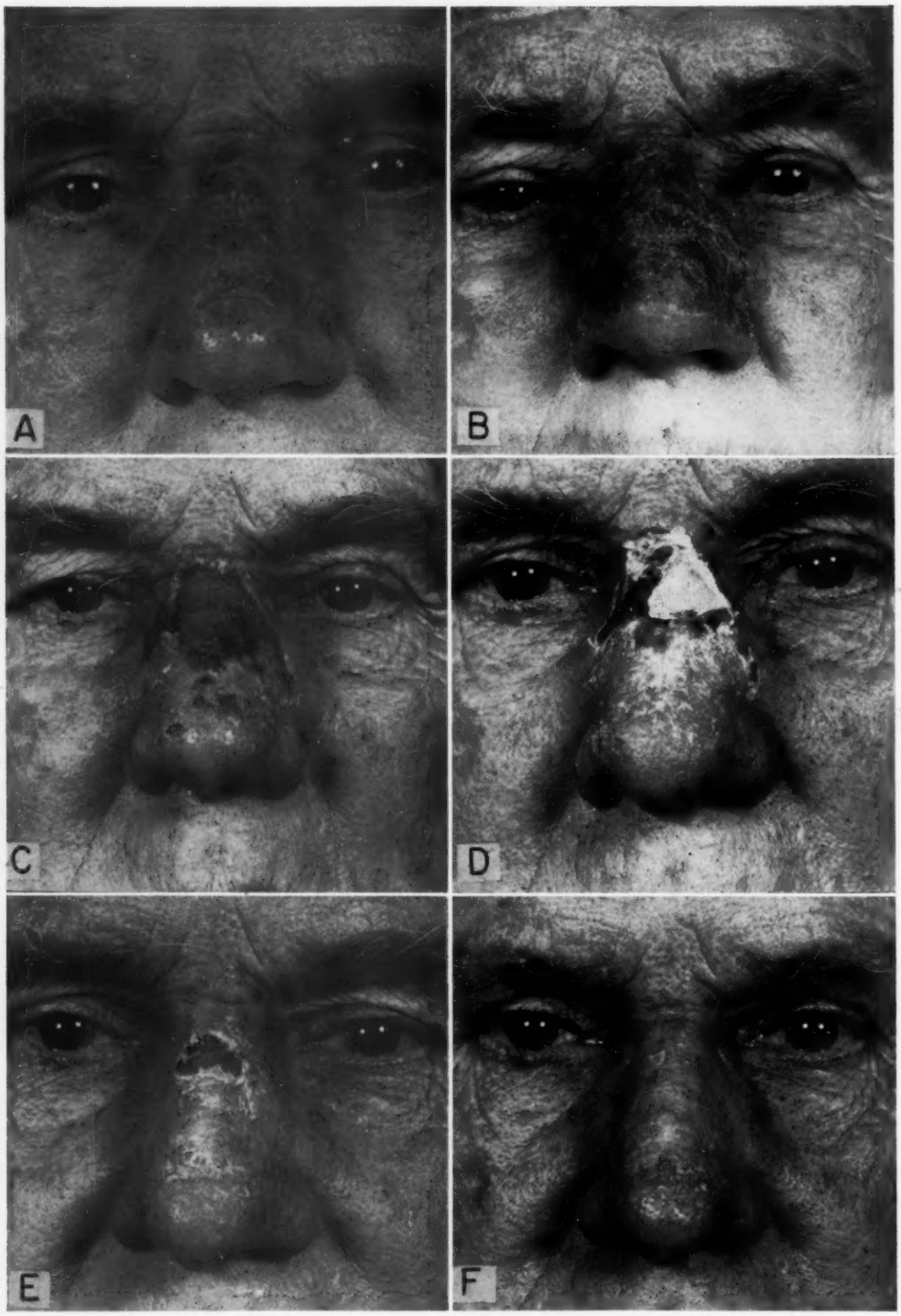

FIG. 15. Case v. Lead-backed patch, 25 cm.^{2}. (*A*) Eleven days. The erythema is moderate and a fine scale is present. The nose is slightly swollen from radiation edema. No photograph was taken before treatment. (*B*) Eighteen days. The reaction is moderately severe and moderately thick yellow crusts cover the treated area. A severe peak reaction had occurred two days before. (*C*) Four weeks. The erythema is subsiding with considerable marginal healing. The upper half of the nose is covered by a thin pseudomembrane. (*D*) Five weeks. The crust is thicker and smaller. The remainder of the nose is covered by a dry scale. The erythema had subsided. (*E*) Seven weeks. The crust is much smaller. The scaling decreased appreciably. (*F*) Ten weeks. Except for slight depigmentation the new skin has a normal appearance. A few scales are present.

Fig. 16. Case VI. Lead-backed patches, 7.2 and 42.6 cm.^{2}. (*A*) Prior to patch therapy. (*B*) Eighteen days Acme. The reaction is severe and the crust is thick. (*C*) Four weeks. Healing is in progress from the margins. A heavy pigmentation ring is at the periphery of the larger area. (*D*) Ten months. The pigmentation ring has faded. The beard is partially epilated. Part of the skin appears normal and part has undergone a mild pale pink atrophy.

Initial Observation. A mild to moderate erythema was present on removal of the patches. *Eight days*. The erythema became moderate to moderately severe and crusts had formed. *Eighteen days* (Fig. 16*B*). This was the acme of the reaction. The erythema was severe and the crusting was heavy. *Three weeks*. The reactions were receding and healing started from the margins. The crusts remained thick. *Four weeks* (Fig. 16*C*). Marginal healing continued. A ring of pigmentation formed about all of the lesions. *Five weeks*. The crusts were smaller. The pigmented rings increased in size. *Ten weeks*. The healing was complete. Part of the treated areas had normal skin and part showed a slight pale pink atrophy. The pigmentation rings were fading. Most of the beard had regrown. *Ten months* (Fig. 16*D*). The pigmentation rings had faded. The beard had partially epilated. The skin changes were about the same as at ten weeks.

CLINICAL OBSERVATIONS

There were 91 patches applied to 12 patients. Observations were made from July, 1953 to June, 1956. Some of the patients were followed closely, others were seen less frequently. Followup examinations were dependent upon the cooperation of the patients and the distance from the hospital. Thus, there were differences in tne number of observations at points of interest during the course of the study.

Technical and physical studies paralleled the clinical observations, hence the method

TABLE I

PREPARATION OF PATCHES

Method	Dose μc hr.	Backing	Number
A. Multiple Drop	4,000	Air	14
B. Edge Immersion Individual Patches	4,000	Air	35
C. Immersion Large Squares	4,000	Air	9
D. Immersion Large Squares	2,500	Lead	33
Total			91

of preparation of the patches varied from time to time as shown in Table I.

In the analysis that follows, a continuous spectrum of acute and late changes from patch therapy was arbitrarily graded by the senior author into six categories: no change (o), threshold (±), mild (+), moderate (++), moderately severe (+++), and severe (++++). For the most part, no statistical significance can be ascribed to any differences in the data. However, it is felt that information of clinical value was obtained. All observations were for patches emitting a dose of 4,000 μc hr./cm.^{2} with air backing or its equivalent of 2,500 μc hr./cm.^{2} with lead backing. The data obtained had not been reported before.

ANALYSIS OF REACTIONS

I. **Acute Changes.** The data are based on 49 observations for initial erythema and 62 observations for maximal reactions.

1. *Initial Erythema, Relation to Method of Preparation.* For simplicity, the patches listed in Table I are classified as having either air or lead backing. Thirty-three of 49 initial observations were made upon removal of the patch. The others were seen within two days. Sixteen were for air backing and 33 for lead backing. All but 6 had an erythema when first observed. These were with lead backing. Four of them were applied to heavily cornified lesions and the reaction was delayed until the fourth day. The other 2 had an erythema on the day following the initial observation. It is thus concluded from the data at hand that in most cases the erythema develops under the patch and is revealed by its removal.

TABLE II

INITIAL ERYTHEMA, RELATION TO PREPARATION

Method	Severity of Initial Erythema				Observations
	o	±	+	++	
Air Backing	0	8	1	7	16
Lead Backing	5	3	19	6	33
Observations	5	11	20	13	49

The distribution for the severity of the initial erythema for air and lead-backed patches is shown in Figure 17a and Table II. Mild reactions predominated with the lead-backed ones, but with air backing, the reactions were nearly equally divided between threshold and moderate. These findings suggest that there is no significant difference between the two methods and the average curve approximates the distribution.

2. *Initial Erythema, Relation to Patch Size* (Fig. 17b, Table III). Allowing for the number of observations, no significant relation was found between patch size and severity of the initial erythema.

3. *Initial Erythema, Relation to Treatment Time* (Fig. 17c, Table IV). The treatment times were divided into a short

TABLE III

INITIAL ERYTHEMA, RELATION TO PATCH SIZE

Size (cm.^{2})	Severity of Initial Erythema				Observations
	o	±	+	++	
<5	3	3	6	3	15
5–9.9	1	4	4	4	13
10–19.9	1	2	4	1	8
20+	0	2	6	5	13
Observations	5	11	20	13	49

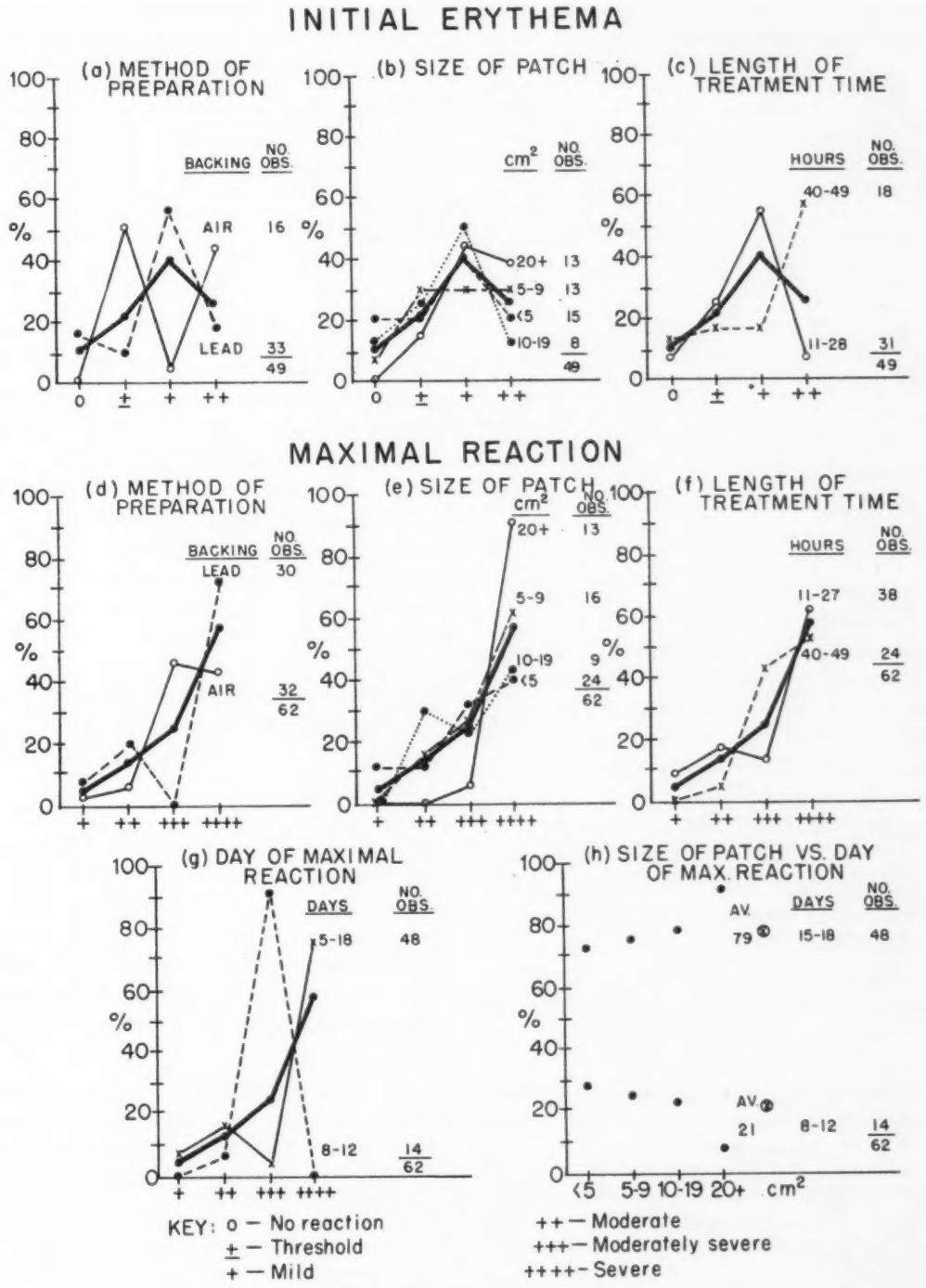

Fig. 17. Graphic presentation of the relation of the various factors to acute changes. The heavy line represents average distribution. (See text.)

TABLE IV

INITIAL ERYTHEMA, RELATION TO TREATMENT TIME

Time (hr.)	Severity of Initial Erythema				Observations
	0	±	+	++	
11–28	3	8	17	3	31
40–49	2	3	3	10	18
Observations	5	11	20	13	49

period (eleven to twenty-eight hours) and a long period (forty to forty-nine hours). Mild erythema predominated for the short times and moderate erythema for the long ones. The difference may be attributed to the longer time for the reactions to develop under the patches of the latter group. This could have been established by observations of all reactions at forty-nine hours (the longest treatment time in the study), but this was not done.

4. *Maximal Reaction, Relation to Method of Preparation* (Fig. 17d, Table V). Most of the acmes for lead-backed patches were severe, whereas they were evenly divided between moderately severe and severe reactions for the air-backed ones. Allowing for reading errors and the number of observations, the differences are probably not significant, and the distribution may be best expressed by the average curve.

5. *Maximal Reaction, Relation to Patch Size* (Fig. 17e, Table VI). The increased incidence of severe maximal reactions for patches larger than 20 cm.^{2} suggests that there is a relationship between the acme and size. This was not observed for patches smaller than 20 cm.^{2}.

6. *Maximal Reaction, Relation to Treatment Time* (Fig. 17f, Table VII). The short period (eleven to twenty-eight hours) and the long one (forty to forty-nine hours) had about the same incidence of severe acmes but there were more moderately severe reactions for the longer treatments. However, the probabilities are that there is no difference and the distribution follows the average curve.

7. *Maximal Reaction, Relation to Day of Acme* (Fig. 17g, Table VIII). The moderately severe acmes occurred in eight to twelve days, whereas the severe ones appeared in fifteen to eighteen days. Allowing for the small number of observations in the eight to twelve day group, this suggests that the lesser reactions reach their peak

TABLE V

MAXIMAL REACTION, RELATION TO PREPARATION

Method	Severity of Maximal Reaction				Observations
	+	++	+++	++++	
Air Backing	1	2	15	14	32
Lead Backing	2	6	0	22	30
Observations	3	8	15	36	62

TABLE VI

MAXIMAL REACTION, RELATION TO PATCH SIZE

Size (cm.^{2})	Severity of Maximal Reaction				Observations
	+	++	+++	++++	
<5	3	3	8	10	24
5–9.9	0	2	4	10	16
10–19.9	0	3	2	4	9
20+	0	0	1	12	13
Observations	3	8	15	36	62

TABLE VII

MAXIMAL REACTION, RELATION TO TREATMENT TIME

Time (hr.)	Severity of Maximal Reaction				Observations
	+	++	+++	++++	
11–27	3	7	5	23	38
40–49	0	1	10	13	24
Observations	3	8	15	36	62

Table VIII

MAXIMAL REACTION, RELATION TO DAY OF ACME

Day	Severity of Maximal Reaction				Observations
	+	++	+++	++++	
8–12	0	1	13	0	14
15–18	3	7	2	36	48
Observations	3	8	15	36	62

Table IX

SIZE OF PATCH, RELATION TO DAY OF ACME

Day	Size of Patch				Observations
	<5	5–9.9	10–19.9	20+	
8–12	7	4	2	1	14
15–18	17	12	7	12	48
Observations	24	16	9	13	62

earlier while the greater ones continue to mount in intensity to attain their acmes at a later time. No acme was observed beyond eighteen days in this series. It is more difficult to determine the time of the acme for slight and moderate reactions because the peak intensity is low and not clearly defined.

8. *Size of Patch, Relation to Day of Acme* (Fig. 17h, Table IX). Regardless of the patch size, most of the acmes did not occur until the third week. However, there was a progressive incidence of this as the size increased.

9. *Hair Regrowth, Relation to Recovery.* There were insufficient data to chart hair regrowth following epilation. After recovery from the acute reaction, reappearance ranged from no growth to full restoration. This depends upon the thickness of the skin and the depth of the hair follicles.

II. **Late Changes.** Observations of the late changes are shown in Table x. Data permitting, they include the first and last observations for normals and pink atrophies, and the first observation for white atrophies. Thirty-one normals, 69 pink atrophies and 59 white atrophies are re-

Table X

OBSERVATIONS OF LATE CHANGES

		Observations																	Total	Per Cent
Pink[1] Atrophy	o[4]	3	16		9	1	1											1	31	31.0
	±	1	6	5		6	3	2	1										24	24.0
	+	13	7	4		3		8	1						1			1	38	38.0
	++		2					2										2	6	6.0
	+++						1												1	1.0
	Total	17	31	9	9	10	5	12	2						1			4	100	100.0
White[2] Atrophy	±[5]			6			5						12						23	39.0
	+			2				1		1			3		9				17	28.8
	++							4					4	5		5			18	30.5
	+++												1						1	1.7
	Total			8			5	5		1			2	19	5	9	5		59	100.0
	Months[3]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	

[1] First and last observations recorded, data permitting.
[2] First observation only.
[3] Includes two weeks after the first month, and two weeks before and after each succeeding month.
[4] No change (normal).
[5] Depigmentation only.

corded. Subtotals for the degrees of atrophy are also given. Although the effects of patch therapy were followed for up to two years, they were tabulated for only eighteen months since there were no last observations for normals or pink atrophies, nor first observations for white atrophies after that time. There was one normal reading after six months and four pink atrophies after eight months. Only one moderately severe change was seen for both types of atrophy. There was no severe atrophy or scarring in two years. All showed re-epithelization. Variations in atrophy are primarily related to connective tissue changes in the dermis.

The curves in Figure 18 illustrate the distribution for the appearance and dis-

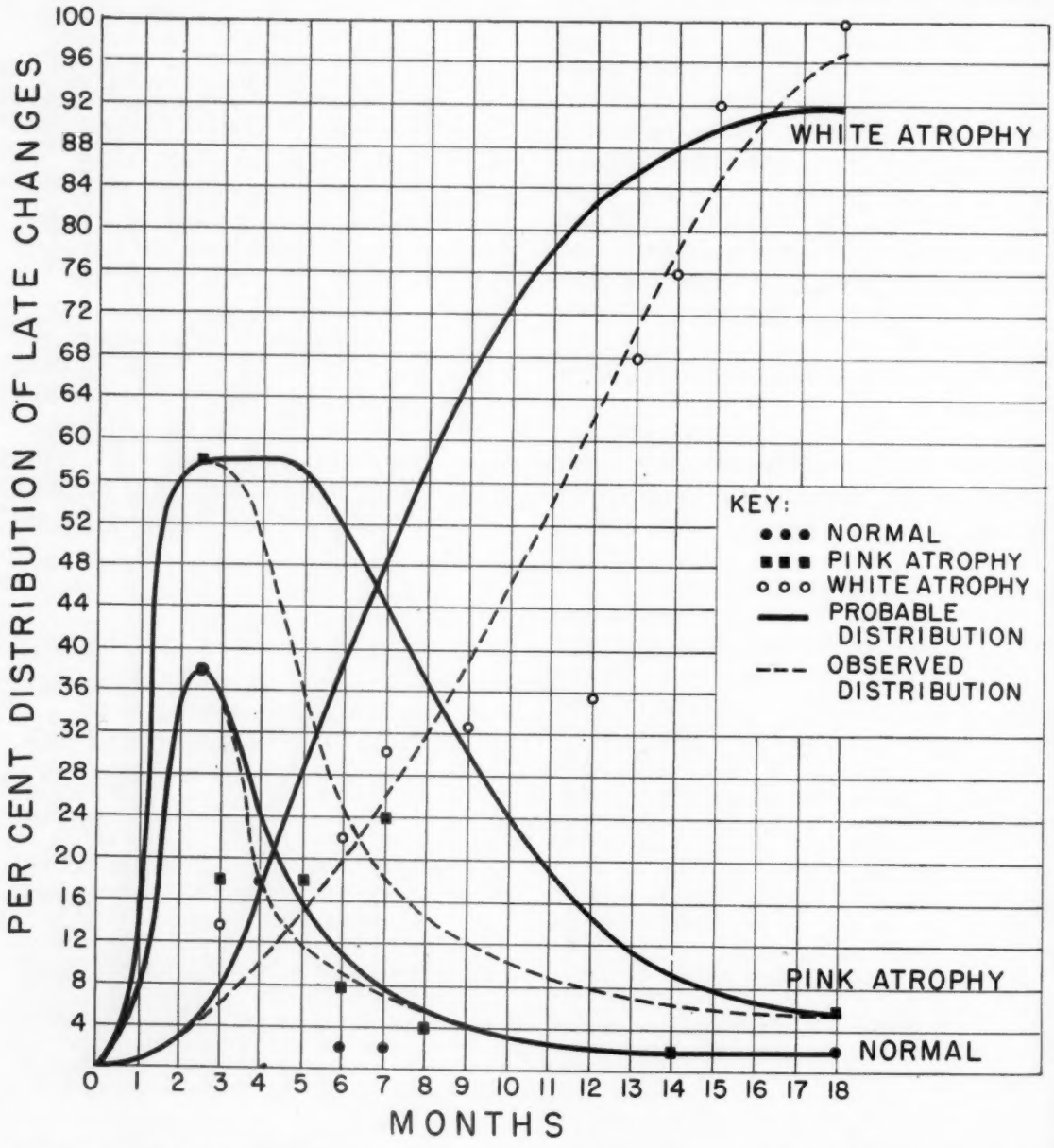

FIG. 18. Distribution of normals and late changes after recovery from the acute effects of patch therapy. The solid lines represent the probable distribution and the dotted lines the observed distribution. The curves for normal and pink atrophies complement each other since both undergo direct transition to white atrophy. The period of maximal transition is three to ten months.

appearance of normals and pink atrophies, and the appearance of white atrophies. Since there was direct transition from normals to white atrophies, without an interval of pink atrophy, their curves complement each other and their summation was considered in the transition to white atrophy. Curves for observed and probable distribution are shown. The latter group is displaced to the right for normals and pink atrophies and to the left for white atrophies to account for the time that the normals and pink atrophies persisted after the last observation and the white atrophies were present before they were first seen. The period of maximal transition is from three to ten months.

In general, there was a mild progression in atrophy with transition from pink to white. The normals would become depigmented or show mild white atrophy. Progress in white atrophy was slow during the two year period of the study. Occasionally, telangiectases appeared.

1. *Pink Atrophy, Relation to Patch Size* (Fig. 19a, Table XI). Except for a reverse in the incidence of no reactions (normals) and threshold changes, the curves for patches larger and smaller than 20 cm.^{2} are similar. The differences are not significant.

2. *Pink Atrophy, Relation to Maximal Reaction* (Fig. 19b, Table XII). Although all but the severe acmes are inadequate in number, the findings indicate that the moderately severe and severe acmes are more likely to develop atrophy than the mild to moderate ones. The relatively greater incidence of mild atrophy for the moderately severe acmes over the severe acmes is probably due to reading errors and the small number of observations.

3. *White Atrophy, Relation to Patch Size* (Fig. 19c, Table XIII). There are only four large patches. The probability that the distribution for them is due to chance is high and no conclusions can be drawn in the relation of patch size to the degree of white atrophy. It is of interest that the large and small patches showed a reversal only between depigmentation and mild atrophy. Comparison with Figure 19a suggests a mild progress in atrophy after transition from pink to white.

4. *White Atrophy, Relation to Maximal Reaction* (Fig. 19d, Table XIV). Nearly all the changes in this group were threshold or mild. Progressive degrees of acme showed a larger proportion of mild atrophy and fewer instances of depigmentation. The only cases of moderate atrophy were with severe acmes. The probabilities are that the distribution of the moderately severe acmes for white atrophy is more nearly correct than that for pink atrophy.

TABLE XII

PINK ATROPHY, RELATION TO MAXIMAL REACTION

Acme	Severity of Pink Atrophy					Observations
	o	±	+	++	+++	
Mild	0	0	0	0	0	0
Moderate	5	1	0	0	0	6
Moderately Severe	1	0	10	0	0	11
Severe	12	9	19	2	0	42
Observations	18	10	29	2	0	59

TABLE XI

PINK ATROPHY, RELATION TO PATCH SIZE

Size (cm.^{2})	Severity of Pink Atrophy					Observations
	o	±	+	++	+++	
<20	27	14	30	4	1	76
>20	4	9	9	2	0	24
Observations	31	23	39	6	1	100

TABLE XIII

WHITE ATROPHY, RELATION TO PATCH SIZE

Size (cm.^{2})	Severity of White Atrophy				Observations
	±	+	++	+++	
<20	22	15	17	1	55
>20	1	2	1	0	4
Observations	23	17	18	1	59

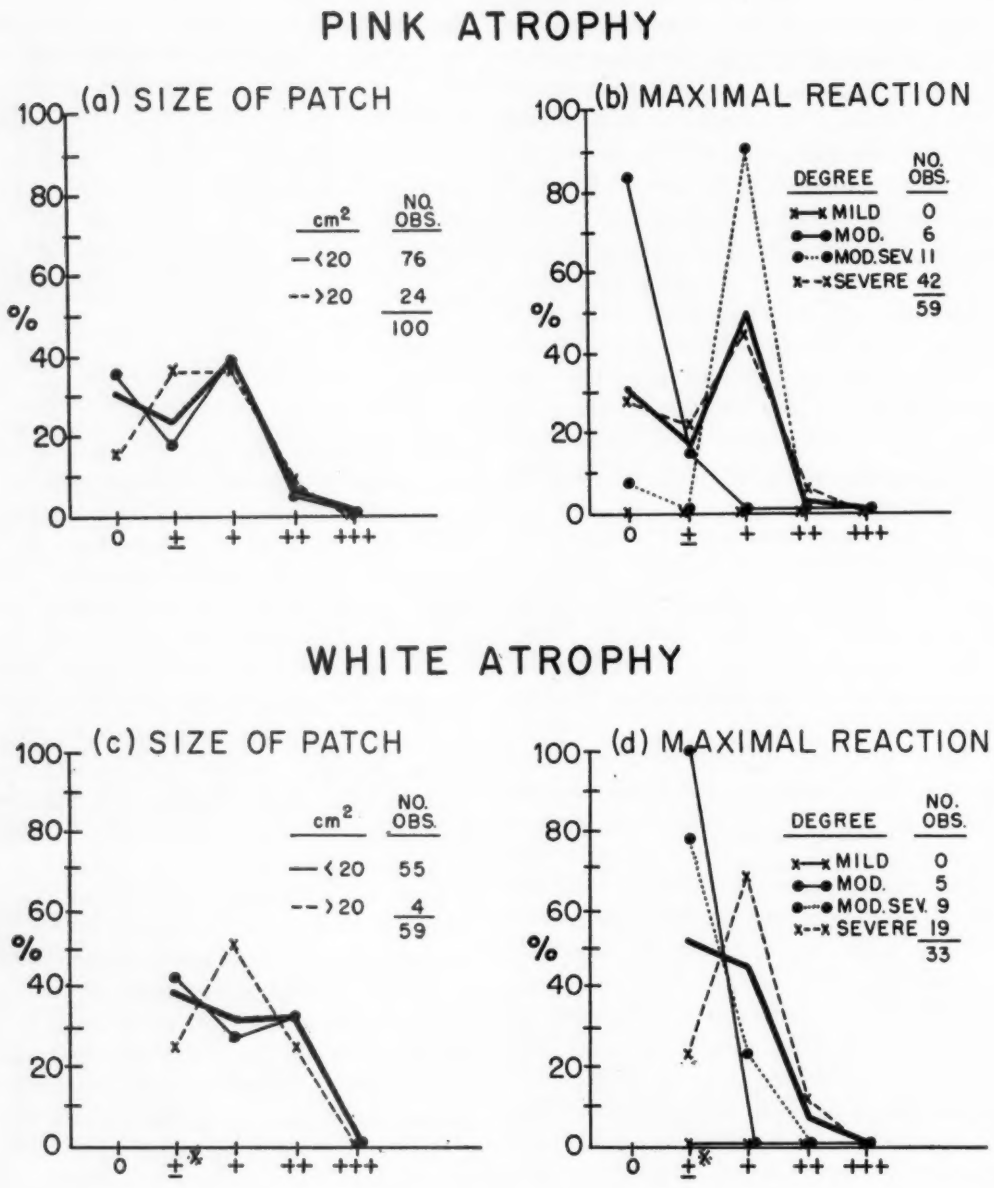

FIG. 19. Graphic presentation of the relation of patch size and maximal reaction to late changes. Note the superimposition of the heavy line curve of average distribution with some of the others. (See text.)

Table XIV

WHITE ATROPHY, RELATION TO MAXIMAL REACTION

Acme	Severity of White Atrophy				Observations
	±	+	++	+++	
Mild	0	0	0	0	0
Moderate	5	0	0	0	5
Moderately Severe	7	2	0	0	9
Severe	4	13	2	0	19
Observations	16	15	2	0	33

GENERAL PATTERN OF SKIN REACTIONS

I. **Acute Phase.** A threshold to moderate erythema usually develops by the time that either the air-backed or lead-backed patch is removed. This indicates a massive response to a large dose, since a surface dose of 2,000 r roentgen-radiation requires at least a week before a threshold erythema appears.

First Week. The erythema increases progressively. Tiny vesicles are occasionally observed. By the end of the week, yellow serous exudate from weeping vesicles begins to dry and form crusts, and the erythema becomes moderate to moderately severe. The patient complains of burning from the reaction.

Second Week. The lesion is covered by thicker crusts. Itching may accompany the burning. Sedation and aspirin are sometimes necessary if large and numerous lesions are treated. The acme may occur by the end of this week.

Third Week. The acme usually occurs during the first half of the week, frequently on the eighteenth day. Peak reactions are generally more severe than those occurring in the second week. The crust is thick and fills the lesion to the edge. A bullous epidermolysis instead of crusting was observed on the dorsum of the hands and on the forearm of 2 patients. The day after the acme, there is a slight but perceptible decrease in the reaction indicating a definite end point, and the patient notes a lessening in itching and a cessation of burning. By the end of this week the turning point is quite evident. The hair is lost and, in some cases, pigmentation appears at the periphery.

Fourth to Ninth Week. Healing occurs from the margin and the erythema fades. The crust sloughs away from the edge toward the center, revealing new skin. It completely separates between the sixth and ninth weeks. The new skin is pink and mildly atrophic or normal and occasionally depigmented. The peripheral pigmentation, if present, fades and there may be regrowth of hair if the follicles are deep enough.

II. **Late Phase.**

Nine Weeks to Six Months. Pink atrophy may or may not progress. This largely depends upon the texture and thickness of the skin. The pink color is due to hyperemia from injury to capillaries and the atrophy is related to changes in the connective tissue of the dermis. The epidermis has regrown from the margins and from adnexal structures beyond the effective range of the irradiation. The skin may become as thin as tissue paper, particularly if the dermis is normally thin. Skin that does not re-epithelize becomes scarred because the adnexa, which provide islands for new epithelium, are destroyed. There was no scarring in this series. The cheeks tolerate beta rays better than the infraorbital regions. The nose and ears generally show fairly good tolerance.

The lesions that had returned to normal upon recovery from the acute phase usually have progressed to depigmentation or mild white atrophy during this period.

Six Months to Two Years. Pink atrophy fades into white atrophy. During the transition, pink and white areas may be seen. White atrophy is due to endarteritis. The skin becomes avascular and collagen changes occur in the dermis. In the latter part of this period, small telangiectases may appear.

More than Two Years. This period is beyond the scope of our study, but old cases are seen from time to time. White atrophy

may be mild but is usually moderate to severe. Sometimes there is superficial white scarring. Telangiectases are not uncommon (Fig. 20).

DISCUSSION

The advantage of beta ray over roentgen ray therapy, even in the ultrasoft range, for treatment of superficial lesions is the rapid fall off in dose. This minimizes injury to the deep layers of the skin and to the structures immediately beneath it. Beta radiations do not depress the bone marrow and have no systemic effects, except those secondary to acute radiation injuries of the skin from a massive accidental exposure. Since new skin can grow from sweat glands and deep hair follicles beyond the effective range of the beta particles, re-epithelization occurs after large doses sufficient to cause epidermolysis and there is regrowth of hair from the deep follicles. Recovery from the acute reaction and the late skin changes are about the same for large areas as for small ones.

The pure beta emission of radiophosphorus is particularly suitable for superficial lesions. The average energy, 0.69 mev., is higher than the average for the heterogeneous beta radiations from radium plaques emitted through thin foils such as aluminum, monel or silver that cover them. Although the alpha rays are stopped, the gamma ray transmission is virtually unaffected and represents about 3 or 4 per cent of the surface dose. P^{32} soaked in blotting paper or impregnated in plastic sheets as described by Smithers[14] and Sinclair and Blondal[13] is flexible and can be cut to any size and shape in contrast to the fixed sizes of the rigid radium beta plaques. The cross section capture of P^{32} for neutrons is high and solutions of high specific activity are readily available at a relatively low cost. The half life is 14.3 days, and a solution with an activity of 5 mc/ml. can still be used after two half lives. Treatment is limited to lesions about 1 mm. in thickness and thick crusts should be removed, if possible.

The validity of surface dose measurements of beta irradiations in reps is questioned because of the rapid fall off in dose even within the first millimeter, the difference in biologic effectiveness as compared to roentgen rays, and the technical difficulty of achieving accuracy. Low-Beer expressed his doses in μc hr./cm.^{2} and using

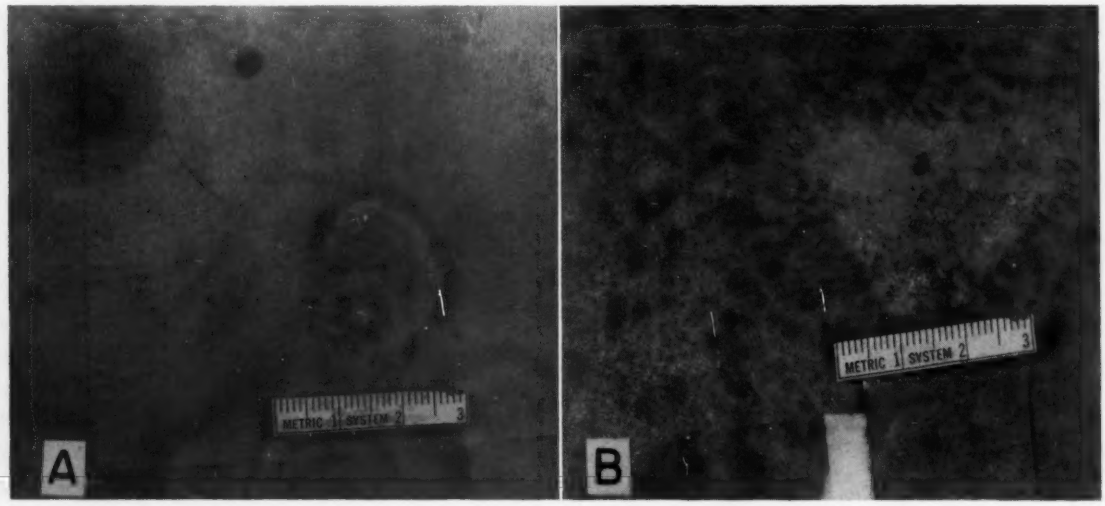

FIG. 20. Late radiation changes from P^{32} patches applied five years before. Preparation was by the multiple drop method. The dose was 4,560 μc hr./cm.^{2} in twenty-four hours. Note the superficial white scarring and telangiectasia. The patient has very radiosensitive skin and developed a radiation ulcer of the ear with a skin dose of 4,500 r roentgen irradiation in five days, half-value layer 2 mm. Al.

the Marinelli formula, he calculated the dose in the first millimeter of skin to be 4.3 r/hr. per $\mu c/cm.^2$ on the basis of absorption measurements in unit density material with P^{32} soaked in 21 $mg./cm.^2$ blotting paper.

Surface dosage rates have been measured by several workers. The most accurate instrument is the Failla extrapolation chamber. This is connected to a Lindemann-Ryerson electrometer and measurements are made by discharge of a condenser in the circuit. In a personal communication to Low-Beer, Loevinger, using this instrument, obtained a surface dose of 8.82 r/hr. per $\mu c/cm.^2$ with P^{32} in 21 $mg./cm.^2$ blotting paper. Using Loevinger's value, we estimate our surface dose to be about 8.5 r/hr. with 25.4 $mg./cm.^2$ blotting paper. Backscatter from 0.01 inch lead raises this by 61 per cent to about 13.7 r/hr. We plan to check these figures with the Failla chamber.

Depth dose measurements were made for our air and lead-backed patches with the Failla chamber using cellophane absorbers. The transmission for lead backing is slightly less than for air backing since the average energy of the reflected beta particles is not as high as those emitted directly from the patch. The loss from self absorption is greater for the beta particles scattered back from the lead since they travel a greater distance through the paper. This reduces the range in the absorbing medium. In Figure 21, our curves are compared with Loevinger's theoretic curve for sources thicker than the maximum beta particle range and with Sinclair and Blondal's curve using water absorption of 55 $mg./cm.^2$ impregnated plastic. The half-value layer in the first millimeter for our air-backed patches is 50 $mg./cm.^2$. For the lead backing it is 43 $mg./cm.^2$. Subsequently, it increases to 70 $mg./cm.^2$ and 60 $mg./cm.^2$, respectively. Figure 22 compares the depth dose curves for air and lead-backed patches with soft and conventional low voltage roentgen rays. Transmission even for the lowest energy contact roentgen rays is considerably higher.

The dose of 4,000 μc hr./$cm.^2$ with air backing and its equivalent of 2,500 μc hr./$cm.^2$ with lead backing is arbitrary and probably excessive for most superficial lesions, but with it we have had no recurrences of the lesions selected for treatment.

Most of the patches developed an erythema under them, revealed upon removal. The majority of initial erythemas for the eleven to twenty-eight hour group was mild. Moderate erythemas predominated for the forty to forty-nine hour group; presumably there was more time for the reaction to intensify under the patch. If forty-nine hour observations were made for all of them, there might have been no difference. No significant difference in initial erythema was seen for air or lead backing or for the patch size.

Patches over 20 $cm.^2$ usually produce greater acmes than smaller ones. Most of the acmes occurred in the third week, the incidence rising as the patches increase in size. Except for one acme at eight days, the maximal reactions appeared in twelve to eighteen days. About 80 per cent of the acmes were either moderately severe or severe. The day that these occurred was easy to determine since there was usually a slight but perceptible decline in reaction on the next day. This was difficult to assess for mild and moderate acmes; however, the lesser reactions probably reach their peak earlier than the greater ones. No significant difference in the acme was observed for air and lead backing or for treatment time.

Recovery from the acute reactions occurred by the ninth week. About 40 per cent of the lesions healed with normal skin and 60 per cent with pink atrophy. The period of maximal transition to white atrophy was three to ten months. White atrophy progressed slowly during the two year period of the study. Occasionally, telangiectases appeared. There were no changes beyond moderately severe atrophy in the study, but occasional old cases were seen that had severe white atrophy or

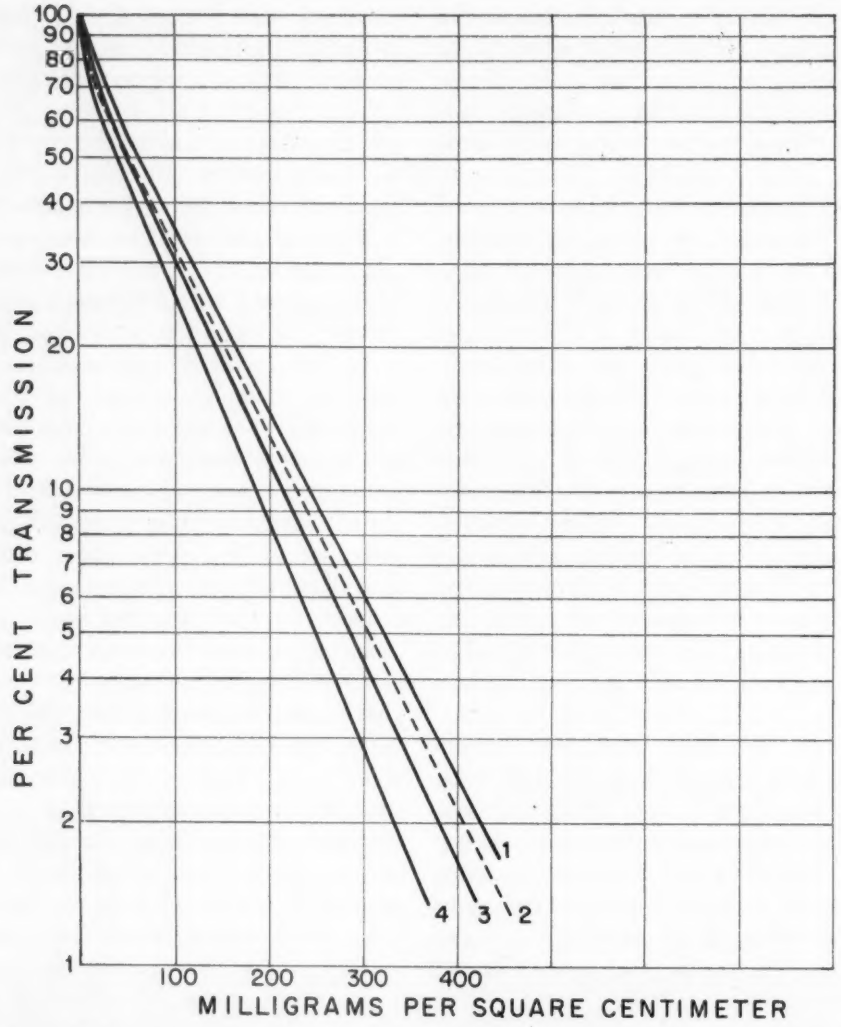

FIG. 21. P^{32} absorption curves in unit density absorbers. 1. Sinclair and Blondal.[13] Pile irradiated 55 mg./cm.^{2} plastic sheeting. Water absorber. 2. Loevinger. Theoretical curve for an infinite thickness source. 3. Roth and Castle. 25.4 mg./cm.^{2} blotting paper, air backing. Cellophane absorber. 4. Roth and Castle. 25.4 mg./cm.^{2} blotting paper, 0.01″ lead backing. Cellophane absorber. The depth dose is slightly less than for air backing due to dissipation of some of the energy of the beta particles reflected from the lead by self-absorption in the paper.

superficial scarring with marked telangiectasia.

No significant relation was observed between patch size and degree of pink atrophy. This was inconclusive for white atrophy, because of insufficient data for large patches. Greater acmes are more likely to produce more pink atrophy than lesser ones, and there is a similar relationship for white atrophy.

SUMMARY

Low-Beer originally described the use of P^{32} on blotting paper for superficial skin lesions. He applied it as evenly as possible with multiple droplets. This is often difficult to accomplish. In addition, it is time consuming and increases the exposure to beta irradiation.

Two modifications are introduced to speed the preparation and improve the dis-

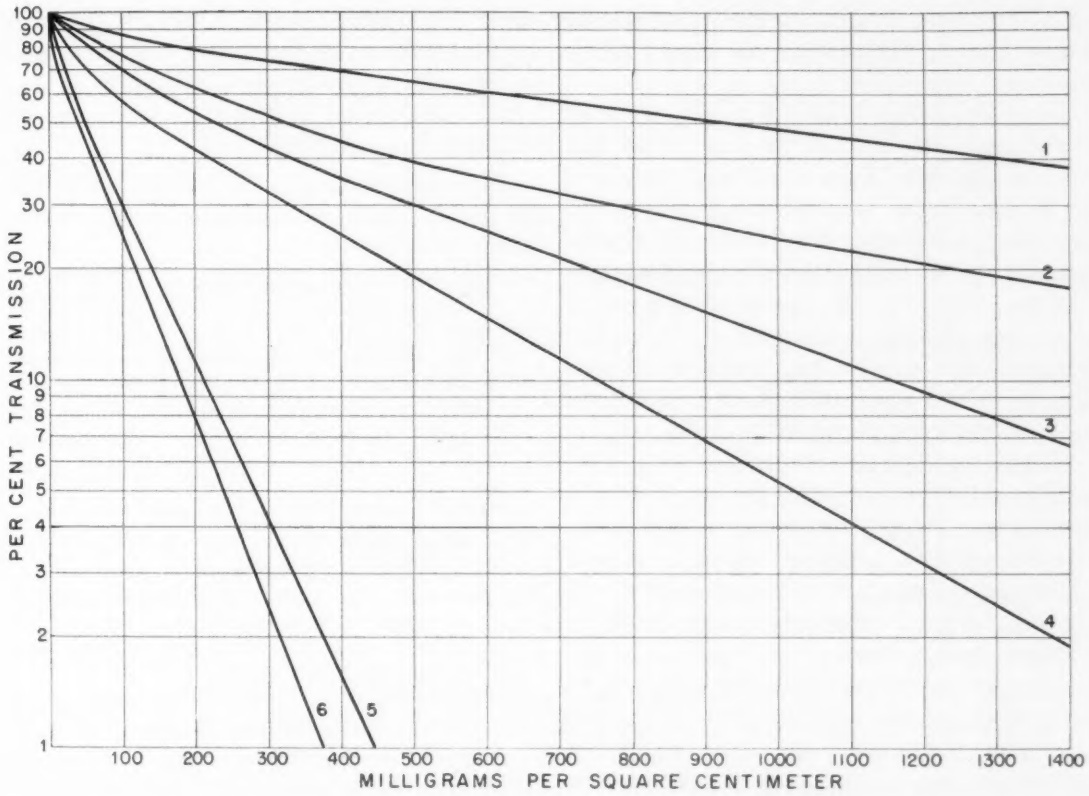

FIG. 22. Comparison of absorption curves of low voltage roentgen rays with P^{32} beta rays in unit density absorbers. 1. 100 kv., focal skin distance 15 cm., half-value layer 1.0 mm. Al (9.3 mm. water equivalent), 2.5 cm. dia. field. (*Brit. J. Radiol.*, supplement No. 5.) 2. 60 kv., focal skin distance 1.5 cm., half-value layer 3.3 mm. Al (3.5 mm. water equivalent), 1.5 cm. dia. field. Chaoul contact unit. (*Brit. J. Radiol.*, supplement No. 5.) 3. 50 kv., focal skin distance 2 cm., half-value layer 0.3 mm. Al (2.5 mm. water equivalent), 1.0 cm. dia. field. Phillips contact unit. (*Brit. J. Radiol.*, supplement No. 5.) 4. 30 kv., focal skin distance 2 cm., half-value layer 1.35 mm. skin. Phillips contact unit with a mica beryllium window. (Amdrup and Knudsen.[1]) 5. P^{32} blotting paper patch, air backing, half-value layer 0.5 mm. cellophane, 2.5 cm. dia. source. (Roth and Castle.) 6. P^{32} blotting paper patch, 0.01" lead backing, half-value layer 0.4 mm. cellophane, 2.5 cm. dia. source. (Roth and Castle.) Note the marked difference in depth dose even for the ultrasoft roentgen rays of curve No. 4 as compared to the beta ray absorption curves. All half-value layers are taken from the first part of the curve.

tribution. The first is known as the "edge immersion" method. An edge of a blotting paper patch that has been cut to fit the lesion is immersed in a measured drop of solution of known activity sufficient to saturate it by capillarity. It is dried, autographed and taped to the skin. The second is called "immersion of large patches." A solution of known activity and volume is placed in a three-inch square flat lucite dish. The quantity is just enough to saturate a piece of blotting paper of the same size. Carrier phosphorus and a trace of wetting agent is added to it. This facilitates an even spread of activity. The paper is immersed in the dish, then dried and autographed. Patterns are traced on the outside of a folded lead foil. The activated blotting paper is glued to the inside of the leaf where the tracings were made. Protection is thus provided for the trained worker and the exposure hazard is reduced to about 5 per cent. The patches are cut and the loose foil is discarded. They are then taped to the

skin. The first modification is suitable for single lesions, the second for the large or multiple ones.

Superficial skin cancers and keratoses are treated to 4,000 μc hr./cm.^{2} with air-backed patches. This is reduced to 2,500 μc hr./cm.^{2} with lead backing, due to 60 per cent backscatter from the lead. Transmission is a little less for lead-backed patches than for the air-backed patches since the average energy of the reflected beta particles is not as high as those emitted directly from the patch. Clinically, however, there is no perceptible difference.

The advantage over roentgen irradiation is that injury to the deep layers of skin is minimized. Except for the fact that large patches tend to produce greater maximal reactions, the acute reaction, recovery, and late changes are nearly the same for large patches as for small ones. In this series, the treatment time varied from eleven to forty-nine hours. This did not affect the character of the reactions significantly. An erythema was usually present when the patch was removed. The peak reactions were from the twelfth to the eighteenth day. Healing occurred by the ninth week. About 60 per cent showed pink atrophy as the initial late change. The others returned to normal. After six months most of the treated lesions had some degree of white atrophy varying from depigmentation to moderately severe changes. Occasionally, telangiectases were seen. Observations for the series were up to two years. Beyond this time an increasing incidence of superficial scarring and telangiectases should be anticipated.

Six cases were reviewed in detail and the data from the series are analyzed for acute reactions and late changes.

Merall Roth, M.D.
14 Via Cheparro Drive
San Rafael, California

ADDENDUM

The usual procedure was to remove the radioactive material deposited on the skin by the patch with soap and water at the end of the treatment. It is now recommended that a thin unit density film such as mylar or saran be cut to the size of the patch and interposed to avoid contamination of the skin. Absorption of the beta radiation by the film is negligible.

The authors express their gratitude to Dr. Robert R. Newell for his counsel in the preparation of this paper.

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THE TREATMENT OF LUNG CANCER (PRIMARY AND METASTATIC) BY RADIOACTIVE PHOSPHORUS ADMINISTERED INTRAVENOUSLY, INTRA-ARTERIALLY AND INTRACARDIALLY*

By IRVING M. ARIEL, M.D.
NEW YORK, NEW YORK

THIS paper describes experiences gained from attempts to obtain palliation in patients with inoperable cancer of the lung, including those with inoperable primary bronchogenic carcinoma and those with metastases to the lung from other primary sites.

Numerous reports attest to the efficacy of irradiation for controlling troublesome symptoms due to inoperable lung cancer. Roentgen therapy has been the modality most frequently employed and one which has given the best results. The administration of a proper dose of roentgen irradiation to the lung entails a prolonged period, necessitating that the patient make frequent trips for treatment or be hospitalized. In a previous study reported by the author, a period of 1.3 months of hospitalization was necessary to administer a palliative course of deep roentgen therapy on an average in 820 patients bearing inoperable lung cancer. The average duration of life at the completion of this therapy was a short span of 2.9 months. This spurred investigators to seek a less traumatic method of shorter duration for offering palliation to these patients. One method attempted by the author to spare patients the trauma and long period of exposure to roentgen rays for their few remaining months was to implant gold radon seeds and needles into inoperable bronchogenic carcinoma discovered to be inoperable at the time of thoracotomy. Each of 17 patients so treated enjoyed palliation, but in each instance the palliation was transient and each patient succumbed from the disease without any significant prolongation of life inherent in this form of treatment. The conclusion was accordingly drawn that this type of therapy was indicated for tumors discovered to be inoperable at the time of thoracotomy, but that thoracotomy was not indicated expressly for the purpose of implanting gold radon seeds and needles interstitially.

More recently, Hahn, Gottesman, Clark and others have injected radioactive gold into inoperable lung cancers discovered to be inoperable at the time of thoracotomy and have obtained palliation. Again the palliation was transient, and it is not considered that the benefit warrants the performance of thoracotomy for the express purpose of injecting the radioactive isotopes.

One other satisfactory method of offering palliation in patients with inoperable lung cancer is the use of one of the nitrogen mustard derivatives. The one which has been found most satisfactory is methyl-bis beta-chloroethyl amino hydrochloride. Numerous reports have commented upon favorable symptomatic response obtained from this therapy, especially in patients with superior vena caval obstruction. Not infrequently patients who are quite ill, suffering from fever, night sweats, anorexia, chest pain, cough, dyspnea, etc., will be relieved from these symptoms by the use of nitrogen mustard. In each instance, however, the symptomatic relief is transient and there seems to be an escape from the benefits derived from this form of therapy.

This study was undertaken to investigate a method of administering irradiation to patients with inoperable lung cancer without subjecting them to the rigors of a course of external irradiation or thoracotomy. The internal irradiation with radio-

* From the Pack Medical Group and the Pack Medical Foundation, New York, New York. Aided by Grant from the Atomic Energy Commission.

active phosphorus was chosen for this purpose. Since the first report of radioisotope therapy for leukemia, by Lawrence, Scott and Tuttle[9] in 1939, there have been many reports describing the distribution of this isotope in the human body. When radiophosphorus is introduced by the oral route, there is a loss of about 25 to 50 per cent due to failure of absorption. Accordingly, the isotope was administered intravenously in all instances of this series. Radiophosphorus administered by the intravenous route is excreted almost exclusively by the kidney. By the end of the third day approximately 25 per cent of the given dose has been excreted, and by the end of the seventh day approximately 1 per cent of the administered dose is excreted per day. Because of these observations a course of therapy was given to the patients under investigation, consisting of an average of 5 mc of P^{32} repeated in a week for an average total dose of 10 mc. Some of the patients studied were so ill that only 5 mc of P^{32} was administered as a total dose.

This report describes results of observations designated to show the following:

1. The effects of radioactive phosphorus upon the alleviation of symptoms of patients bearing pulmonary cancer, either primary or metastatic.

2. The effect of this form of therapy upon longevity.

3. A measurement designed to note whether there is a collective uptake of the isotope by the tumor in excess of that of normal pulmonary tissue.

4. Attempts to enhance the concentration of the isotope by: (a) injecting the isotope directly into the heart, thereby possibly avoiding some of the dilution which may occur; (b) noting the effect of a preliminary course of nitrogen mustard upon the selective uptake of the isotope by the tumor; and (c) noting the effect of administering the radiophosphorus intra-arterially.

METHODS

In all instances the patient was ambulatory, and only those were chosen who had exhausted all other forms of therapy. Diagnosis was established by biopsy in almost all instances. In 1 or 2 patients the clinical evidence was overwhelming and no biopsy was obtained. The isotope was given in the form of radiophosphate as sterile isotonic sodium phosphate solution which had been brought up to a pH of 7 and diluted with normal saline solution. Approximately 1 cc. was made to contain 1 mc of phosphorus on the day of administration, and an average single dose of 5 mc of P^{32} was given. The dose was repeated, usually, one week later. In some instances a single dose of 10 mc was given.

In those patients in whom the effect of intracardiac administration of P^{32} was investigated, a polyethylene catheter was inserted into the antebrachial vein and the P^{32} delivered into the right auricle. The position of the catheter was determined by fluoroscopic guidance. One liter of solution containing 10 mc P^{32} was given by slow drip method which required from twelve to twenty-four hours to administer.

Where the effect of intra-arterial administration was investigated, a polyethylene catheter was inserted into the femoral artery to the level of the thoracic aorta. The catheter was left *in situ* and 10 mc P^{32} injected directly into the thoracic aorta, hoping that the isotope would reach the lung tumor via the bronchial arteries. Tourniquets were placed on both thighs during the period of administration and shortly thereafter in an effort to minimize the deposit of the isotope in the extremities.

In 5 patients a course of radioactive phosphorus therapy was instituted and measurements made. At a variable time later (about one month) 10 mg. of nitrogen mustard was given intravenously, and five to seven days later another dose of radioactive phosphorus was given intravenously to note if the chemotherapeutic agent might in any way influence the uptake of the radioactive phosphorus by the tumor tissue.

Method of Determining Quantity of P^{32} in Lungs. The counting was performed by placing the scintillation counter almost in direct contact with the skin over various

predetermined regions of the chest cavity. A point of reference was taken over the pretibial region of both legs and the calculations of the concentration of the radioactive isotope, in the different locations of the lung, made on the basis of the amount counted above that of the point of reference. Although Bremsstrahlung from inelastic collisions of beta rays with nuclei undoubtedly contribute to the count, it is not believed that these interfere significantly with the appraisal as to the quantity of the isotopes present in the underlying tissues. All values are expressed in terms of percentage pick-up by the lung tissue above that noted at the point of reference. The determination of the beta rays emitted by the P^{32} was made with an NRD Radimax sodium iodide crystal scintillation counter (manufactured by NRD, St. Louis, Missouri). These counters utilize the "plateau" of the photomultiplier without artificial voltage control in the counter. The efficiency for P^{32} is approximately 100 per cent. The aperture is three-fourths of an inch in diameter and is shielded by lead. The counter was placed one and five-eighths inches from the skin. The scaler used was an automatic Tracerlab SC-33 "1000" scaler.

In most instances a complete blood cell count and other determinations of blood chemistry were performed before instituting the isotope therapy and at frequent intervals afterward. In the subsequent tables, if other medications had been given to the patients which interfered with determining the effects of the P^{32} upon the hematopoietic system, the values for the blood elements are not listed.

RESULTS

The results are tabulated in the tables. Tables I to V present the clinical responses to the intravenous radioactive phosphorus. The data of those patients treated for primary inoperable lung cancer are shown in the first table. The subsequent four tables present the results obtained for patients with cancer metastatic to the lungs. The data of 51 patients are included. An additional group had received P^{32} therapy for pulmonary cancer, but these studies were complicated by the fact that other concomitant medications were given, or the patients could not be followed up, or, in some instances, the medication was given to a preterminal patient and the data were used for obtaining the effects on the pick-up of P^{32} by lung tissue. Nothing could be gained by attempting to estimate any clinical response except to state that none occurred.

Patients with Primary Inoperable Lung Cancer. Table I presents the clinical data of 10 patients with primary lung cancer. Eight of these patients suffered from bronchogenic carcinoma. In 1 the diagnosis of a malignant bronchial adenoma had been established. The additional patient was a fourteen year old boy who had a neuroblastoma of the mediastinum which directly infiltrated the left upper lobe. He had been treated previously with interstitial radioactive gold and was asymptomatic when observed by us. He was given a small dose of 4 mc of P^{32} with no clinical or hematologic response, either beneficial or detrimental. The patient remains well over one year after treatment.

Of the 8 patients with bronchogenic carcinoma, 1 remains well six years after the initial symptoms and one year after the administration of the radioactive phosphorus. He had been treated previously with deep roentgen therapy. The additional 7 patients have all succumbed of the cancer an average of three months after the administration of radioactive phosphorus.

We accordingly surmise that there has been no appreciable benefit from the standpoint of longevity upon patients with inoperable bronchogenic carcinoma. It must be recalled that each of these patients had received previous treatment, including thoracotomy, deep roentgen therapy and/or intravenous or intrapleural nitrogen mustard therapy. Hence, it is not too surprising to note no marked benefit from the isotopic irradiation. A number of the patients enjoyed relief from symptoms but in each instance the relief was of a transient

TABLE I

THE EFFECTS OF INTRAVENOUS P^{32} UPON PATIENTS WITH INOPERABLE PRIMARY LUNG CANCER

Patient Age	Sex	Diagnosis	Previous Treatment	Dose of P^{32} Intravenously	Immediate Symptomatic Response	Effect upon Hematopoietic System		Effect Noted on Roentgenographic Appearance	End Results	Remarks
						Before	After			
I.S. 53	M	Diffuse bronchogenic cancer, right lung	Deep roentgen therapy 3 months previously	10 mc	Marked relief of cough following each dose of P^{32}. No effect on dyspnea	Hb. 13.8 RBC. 4.8 WBC. 1,140	13.1 4.5 14,800	No effect	Died 5 mo. later	No selective pick-up
H.B. 62	M	Bronchogenic cancer, right lung	Patient refused operation. Deep roentgen therapy, 300 r×2, 1949. Repeat roentgen therapy, 2,100 r, 12-7-50.	5 mc	Marked relief of chest pain. Patient asymptomatic 1 year later (now)	Hb. 11.2 RBC. 3.6 WBC. 3,500 Differential: Normal	11.3 3.9 8,050 Differential: Normal	No effect	Patient well 6 yr. after onset of symptoms; 1 yr. after P^{32}	Asymptomatic
J.C. 40	M	Bronchogenic cancer, Grade 3	Exploratory thoracotomy, 2-1-53. Million volt roentgen therapy, 2-14-53.	9.2 mc	Slight relief of asthmatic-like wheezes. No benefit for most part	Hb. 9.3 RBC. 4.6 WBC. 4,350	88 4.5 18,300	Further evidence of chest metastases	Died 2 mo.	Improvement from million volt roentgen therapy, 10 mc P^{32} given in preterminal state
A.G. 55	M	Bronchogenic cancer, anaplastic left upper lobe	Deep roentgen therapy	20.6 mc	Relief of pain and dyspnea. Weakness persists after each injection	Hb. 9.8 RBC. 3.4 WBC. 7,500	10.1 3.6 12,200	None	Died 3 mo. Heart failure. Generalized metastases	P^{32} given in preterminal state
M.K. 14	M	Neuroblastoma of mediastinum infiltrating lung, left upper lobe	Interstitial radioactive gold	4 mc	Patient asymptomatic at time of therapy. No effect	No change	None	None	Patient remains well	
Y.L. 62	F	Bronchogenic cancer with hydrothorax, left lung	Intrathoracic HN_2	5 mc	Relief for 2 days of chest pain	Hb. 12.7 RBC. 4.4 WBC. 10,600	13.8 4.5 5,000	None	Died 8 mo.	No benefit
V.M. 62	M	Bronchogenic cancer with cutaneous metastases	—	5 mc	No improvement	—	—	None	Died 2 mo.	Patient was in an extremely poor state when P^{32} was given. No effect
W.S. 53	M	Sarcoma, right upper lung	Lobectomy and postoperative roentgen therapy	10 mc	No improvement	None	None	None	Died 1 mo.	Patient in preterminal state
P.V. 74	M	Malignant bronchial adenoma	Roentgen therapy postoperative, P^{32}, million volt roentgen therapy, 2,100 r×2	10 mc	Improvement with decrease in cough, pain and sputum	Hb. 12.7 RBC. 4.6 WBC. 8,600	10.3 3.4 5,250	None	?	
D.S. 56	F	Diffuse bronchogenic cancer	Deep roentgen therapy	10 mc		None	None	Worsened hydrothorax	Died 1 mo.	Metastases to bone marrow

Patient Age	Sex	Duration of Disease	Last Previous Therapy	Initial Therapy	General Condition	Total Dose	Immediate Symptomatic Response	Effect on Hematopoietic System		Effect on Roentgenographic Appearance	End Results from Time of Initial P^{32} Treatment	Remarks
								Before	After			
D.S. 56	F	Diffuse cancer bronchogenic	Deep roentgen therapy	10 mc		None	None		Worsened hydrothorax	Died 1 mo.		Metastases to bone marrow
E.B. 57	F	12 yr.	—	Mastectomy, 1942	Fair. Marked Dyspnea	5 mc	Relief of dyspnea for 1 week	Hb. 13.5 RBC. 4.6 WBC. 9,800	12.4 4.0 11,350	None	Died 3 mo.	Transient relief of dyspnea which recurred and remained uncontrolled until death
M.B. 70	F	1 yr.	None	None	Poor	8.4 mc	Relief of chest pain	Not determined		None	Died 4 mo.	Patient also had osseous metastases. Questionable benefit
M.C. 56	F	18 yr.	Roentgen therapy to chest wall	Left mastectomy, 1937. Right mastectomy, 1946	Fair	10 mc	Marked relief of chest pain and slight relief of dyspnea	Hb. RBC. WBC.	14.2 4.5 5,150	None	Patient remains well 18 mo. after P^{32} treatment	Unusual instance of bilateral pulmonary metastases occurring many years after mastectomy. Marked relief of chest pain from P^{32} which continued, but slight relief of dyspnea was transient
C.E. 26	F	1 yr.	Roentgen therapy to chest wall region	Radical mastectomy	Fair	6.2 mc	None. Severe dyspnea persists	None		None	Died 3 da.	Extensive pulmonary mediastinal metastases. Showed no response whatsoever to isotope therapy
J.F. 41	F	4 yr.	Roentgen therapy to chest and bones	Radical mastectomy	Good	9 mc	Relief of chest pain. Slight relief of dyspnea. Relief of bone pain	Hb. 11.4 RBC. 3.9 WBC. 4,600	11.1 3.7 7,000	None	Patient remains well 1 yr. after P^{32} treatment	Occasional bone pain only present symptom
M.H. 64	F	1 yr.	None	Mastectomy	Poor	5 mc	Relief of cough and hemoptysis for 1 month	Hb. 14.8 RBC. 4.2 WBC. 5,800	13.7 4.4 4,850	None	Died 8 mo.	Postisotope therapy of HN_3 and deep roentgen rays had no effect
I.L. 47	F	13 yr.	Roentgen therapy to dorsolumbar spine	Mastectomy and postoperative irradiation	Poor	6.9 mc	Slight relief of bone pain. Patient had no chest symptoms	Hb. 11.0 RBC. 3.8 WBC. 7,800	13.2 4.0 5,750	None	Died 10 mo.	Patient developed multiple osseous fractures
E.L. 47	F	2 yr.	None	Radical mastectomy. Postoperative irradiation	Good	8 mc	Transient relief of dyspnea	Hb. 13.8 RBC. 4.4 WBC. 10,500	12.6 4.2 3,000	Continued spread of disease	Died 2 mo.	P^{32} had no effect. Patient became nauseated from P^{32}
E.R. 42	F	3 yr.	HN_3 therapy. Testosterone	Mastectomy	Fair	6.9 mc	Relief of pain and anorexia for 2 months	Hb. 11.5 RBC. 4.0 WBC. 9,800	13.5 4.5 9,300	None	Died 3 mo.	Temporary symptomatic relief. No effect on course of disease
B.S. 38	F	2 yr.	Roentgen therapy	Radical mastectomy	Fair	7 mc	None	Not done		None	Patient died 8 mo. later	Patient developed paraplegia from metastases to spine. No benefit from P^{32}

TABLE III

THE EFFECTS OF P^{32} UPON PULMONARY METASTASES FROM PRIMARY CANCER IN THE FEMALE GENITALIA

Patient Age	Sex	Duration of Disease	Last Previous Therapy	Initial Therapy	General Condition	Total Dose	Immediate Symptomatic Response	Effect on Hematopoietic System		Effect on Roentgenographic Appearance	End Results from Time of Initial P^{32} Treatment	Remarks
								Before	After			
Ovarian Carcinoma												
P.G. 57	F	6 mo.	Roentgen therapy	Exploratory laparotomy and roentgen therapy	Poor	10 mc	None	Not determined		None	Died 2 mo.	No beneficial reaction from P^{32}
E.L. 53	F	2 mo.	Roentgen therapy (paracentesis)	Exploratory laparotomy	Poor	6 mc	None	Not measured		None	Died 2 mo.	No benefit
L.M. 52	F	1 yr.	Excision ovarian carcinoma	Excision carcinoma	Poor	9 mc	Slight relief of chest pain	None		None	Died 4 mo.	No apparent benefit
A.S. 45	F	1 yr.	Irradiation	Radical hysterectomy	Poor	12 mc	Softening of liver tumor. No effect on chest mass	Not determined		None	Died 1 mo.	Combined HN_2 and P^{32} produced severe pancytopenia; 40 mg. HN_2 given before P^{32}
F.H. 63	F	7 mo.	Roentgen therapy	Exploratory laparotomy	Good	10 mc	Worsening of symptoms with severe choking and cough	Hb. 11.8 RBC. 3.9 WBC. 5,800	8.9 3.4 7,500	None	Died 1 mo.	Pulmonary symptoms became worse after P^{32}
Uterine Carcinoma												
T.D. 53	F	2 mo.	Roentgen therapy	Panhysterectomy	Good	10 mc	Improvement of chest and bone pain	Hb. 11.4 RBC. 3.9 WBC. 4,800	8.9 3.5 4,000	Increase in size of metastases after treatment	Died 2 mo.	Transient improvement of symptoms but deterioration of general condition
S.K. 60	F	14 mo.	Exploratory laparotomy	Exploratory laparotomy	Fair	10 mc	Good symptomatic response	Not done		None	Living with huge metastasis to liver 11 mo.	Symptomatic relief
R.D. 63	F	1 yr.	Irradiation	Exploratory laparotomy	Poor	10 mc	No benefit	Hb. 11.7 RBC. 4.0 WBC. 6,350	10.2 3.5 5,500	None	Died 10 mo.	No significant benefit
E.G. 58	C	3 yr.	Roentgen therapy	Exploratory laparotomy	Poor	10 mc	No relief of chest symptoms, but relief of bone pain	Hb. 12.3 RBC. 4.1 WBC. 8,250	12.1 4.2 6,400	None	Died 9 mo.	No relief of pulmonary symptoms

TABLE IV

THE EFFECTS OF P^{32} UPON PULMONARY METASTASES FROM PRIMARY CANCER IN THE COLON AND RECTUM

Patient Age	Sex	Duration of Disease	Last Previous Therapy	Initial Therapy	General Condition	Total Dose	Immediate Symptomatic Response	Effect on Hematopoietic System		Effect on Roentgenographic Appearance	End Results from Time of Initial P^{32} Treatment	Remarks
								Before	After			
J.B. 35	M	1 yr.	Roentgen therapy	Sigmoid resection	Fair	10 mc	No effect	Not determined		Worsened	Died 4 mo.	Patient received roentgen therapy to chest as well as isotope therapy. No effect
J.C. 62	M	1 yr.	Roentgen therapy to chest	Sigmoid resection	Fair	10 mc	No change in cough. Burning sensation in chest	Indeterminate		No effect		
J.S. 67	M	6 mo.	None	Ileocolostomy	Poor	9.5 mc	None	Indeterminate		None	Died 1 mo.	Patient in preterminal state with extensive abdominal metastasis and ascites
M.C.R. 66	M	3 mo.	Colostomy	Abdominal perineal resection	Good	13 mc	Mild improvement in cough	No decrease		None	Died 9 mo.	Fair symptomatic transient improvement
T.R. 55	M	2 mo.	Sigmoid resection	Sigmoid resection	Poor	10 mc	Relief of chest pain	Hb. 14.5 RBC. 4.3 WBC. 4,550	12.6 4.0 5,300	None	Died 10 mo.	No significant effect. Patient had extensive abdominal and hepatic metastases
C.R. 62	M	8 mo.	None	None	Fair	7.8 mc	None	Not determined		None	Died 1 mo.	Patient had marked hydrothorax which resisted all therapy
S.M. 57	M	3 yr.	Sigmoidostomy with anastomosis	Sigmoidostomy	Fair	10 mc	None	Hb. 10.2 RBC. 3.5 WBC. 10,950	10.6 3.4 10,600	None	Died 3 mo.	No response
F.G. 45	M	3 yr.	None	Sigmoidostomy with anastomosis	Poor	10 mc	None	Not determined		None	Died 1 mo.	Patient developed intestinal obstruction
S.K. 54	F	4 yr.	Sigmoid resection with anastomosis	Sigmoid resection with anastomosis	Fair	8 mc	Burning in chest	Hb. — RBC. — WBC. —	11.1 3.8 6,000	Not determined	Died 9 mo.	No benefit

TABLE V

MISCELLANEOUS

Patient Age Sex	Duration of Disease	Last Previous Therapy	Initial Therapy	General Condition	Total Dose	Immediate Symptomatic Response	Effect on Hematopoietic System		Effect on Roentgenographic Appearance	End Results from Time of Initial P^{32} Treatment	Remarks
							Before	After			
Genitourinary System Kidneys											
M.H. 60 M	1 yr.	Roentgen therapy to chest	Exploratory laparotomy	Poor	10 mc	No improvement	Hb. 11.2 RBC. 3.9 WBC. 5,300	10.5 3.5 1,700	No improvement	Died 9 mo.	Tumor extremely resistant to all therapy
F.M. 63 F	1 yr.	Nephrectomy	Nephrectomy	Poor	5 mc	No improvement	Hb. 12 RBC. 3.9 WBC. 5,800	10.4 3.6 3,400	Mass increased in size	Died 1 mo.	No improvement
S.S. 60 M	6 mo.	None	None	Poor	10 mc	No improvement	Indeterminate		No change	Died 1 mo.	
H.B. 52 M	5 yr.	Roentgen therapy to kidney region	Right nephrectomy	Good	10 mc	Improvement of chest pain and cough	Not done		No improvement	Died 4 mo.	Patient had received 10 mc P^{32} fractionated doses of 2 mc per wk. before coming here
Testicle (Seminoma)											
D.P. 42 M	1 yr.	Roentgen therapy to chest	Orchiectomy	Good	5 mc	Improved	No change		No change	Patient remains well 1 yr. later	Good symptomatic response from P^{32} and roentgen therapy to chest
						Sarcomas					
Fibrosarcoma											
S.A. 62 M	9 mo.	None	Amputation left leg and wedge excision of metastasis to lung	Poor	10 mc	None	Not done		None	Died 4 mo.	No benefit
Osteogenic Sarcoma											
N.P. 45 F	1 yr.	None	Radical amputation right arm	Fair	10 mc	Relief of chest symptoms for 2 mo.	Hb. 12.9 RBC. 4.3 WBC. 7,500	12.8 4.2 5,400	No improvement	Died 6 mo.	Patient's cough aggravated first 5 da. after P^{32} and then subsided

TABLE V– *Continued*

Patient Age Sex	Duration of Disease	Last Previous Therapy	Initial Therapy	General Condition	Total Dose	Immediate Symptomatic Response	Effect on Hematopoietic System		Effect on Roentgenographic Appearance	End Results from Time of Initial P^{32} Treatment	Remarks
							Before	After			
Unclassified Sarcoma											
M.H. 64 F	1 yr.	None	None	Fair	5 mc	Improvement of cough and dyspnea	Indeterminate		None	Died 11 mo.	Improvement lasted 9 mo. but some improvement due to post P^{32}, HN_2 and roentgen therapy
Primary Unknown											
O.B. 68 M	3 mo.	Roentgen therapy to lung	Right middle lobectomy	Fair	10 mc	Excellent	Hb. 15 RBC. 5.0 WBC. 8,650	12.6 4.0 3,350	None	Died 14 mo.	Excellent response for 8 mo., then rapid deterioration
F.B. 76 F	6 mo.	None	None	Poor	4 mc	Good relief chest pain. Sense of well-being	Hb. 87 RBC. 4.4 WBC. 7,300	82 4.2 15,000	None	Died 3 mo.	Good but extremely transient response
P.S. 56 F	1 yr.	None	None	Poor	10 mc	None	Indeterminate		None	Died 1 mo.	Patient preterminal when given P^{32}
F.S. 54 F	1½ yr.	Roentgen therapy	Exploratory laparotomy	Fair	5 mc	Improvement in dyspnea and cough	Not done		None	Died 4 mo.	Mild but transient improvement
C.Z. 48 M	4 mo.	None	None	Poor	6.8 mc	None	Not done		None	Died 2 wk.	Patient preterminal when given P^{32}

nature. Two patients enjoyed relief from cough, 3 were benefited by a diminution in chest pain, and only 1 had any appreciable relief from dyspnea.

The results of the P^{32} therapy, as noted by roentgenographic studies, revealed no significant effect in any of these patients.

There was no marked diminution in the hematopoietic system of any of the patients treated with the dosages of P^{32} used in this investigation.

Primary Breast Cancer Metastatic to the Lung. Of 10 patients who had had primary breast cancer which had metastasized to the lungs and who received radioactive phosphorus for treatment, 8 have succumbed an average of five months after the treatment. Two patients remain alive and relatively asymptomatic, one twelve months after treatment and the other eighteen months after therapy. Each of these patients enjoyed relief of chest pain and in one patient (M.C.) the relief of chest pain was marked, with slight relief of dyspnea. It is of interest that in each of these patients the metastases were delayed in occurring. In one patient (M.C.) eighteen years elapsed from the onset of the disease, and in the other (J.F.) four years elapsed from the onset of the disease until the patient received P^{32} therapy. No effects were noted upon the roentgenograms in this series of patients as a result of P^{32}. No significant diminution occurred in the red or white blood cell counts. Of the 10 patients, 1 had no symptoms and developed none from the P^{32} therapy; 3 had no relief of symptoms whatsoever, and those who did enjoy relief enjoyed it for a very short period. There were 4 who enjoyed relief from pain, 4 who enjoyed relief from dyspnea, and 1 who enjoyed relief from cough and hemoptysis. These values pertain only to the symptoms and if 1 patient enjoyed benefit from more than one symptom they are included in this tabulation.

Carcinoma of the Female Genitalia Metastatic to the Lungs. The clinical results of 9 patients bearing primary carcinoma of the female genitalia (ovarian and uterine cancer) are presented in Table III. Of 5 patients with ovarian carcinoma which produced metastases to the lungs, all have died an average of two months after the isotope therapy. No beneficial results were noted in the chest roentgenograms. Of these 5 patients, none enjoyed any significant relief of symptoms. In one (A.S.), although there were no improvements of chest symptoms, there was a softening of a liver tumor from the combined effects of nitrogen mustard and P^{32}. The fifth patient (F.M.) had an increase in the degree of symptoms, with severe choking and cough. Of the 4 patients with uterine cancer, 3 have died an average of seven months after treatment, and 1 is alive with a huge metastasis to the liver. This patient had suffered from dyspnea and chest pain and she stated that there was a relief from these symptoms. The results, however, were not very pronounced in any of the patients with uterine cancer.

It is difficult to adjudge any clinical response upon the pulmonary metastases except to say that none were objectively observed. The fact that these patients also had widespread abdominal cancer would vitiate against drawing any conclusions concerning the clinical response from the P^{32} therapy upon influencing the course of patients with only pulmonary metastases from these primary sites.

Patients with Metastases to the Lungs from Primary Cancer of the Colon and Rectum. The effect of P^{32} administration upon pulmonary metastases from primary carcinoma of the colon and rectum is presented in Table IV. Of 9 patients so treated, 1 was lost to follow-up and the additional 8 died an average of four months after treatment with the isotope. No beneficial effects were noted on the roentgenograms. Of the 9 patients, 7 received no symptomatic benefit whatsoever from the treatment. In most of these patients symptoms continued as they had been before P^{32} therapy. In only 2 was there any relief of the symptoms; in 1 there was mild improvement in cough, and in the other there was some re-

lief of chest pain. These patients were further afflicted in all instances by intra-abdominal metastases. No definite conclusions can be drawn upon any objective response from the P^{32} therapy except that these data indicate that there was none.

Miscellaneous Cancer Group. The data of patients in the miscellaneous cancer group are presented in Table v. Four patients with primary carcinoma of the kidney metastatic to the lungs were not appreciably benefited by the P^{32} therapy and each of these died an average of four months after therapy. One patient with a seminoma received deep roentgen therapy to the chest plus 5 mc of P^{32} and this patient remains well and asymptomatic one year later. The effects are undoubtedly the result of roentgen therapy, and nothing can be stated concerning any possible effect of the radioactive phosphorus.

Three patients with sarcomas have each succumbed an average of seven months after the administration of P^{32}. Two of these patients had moderate relief of chest symptoms. One with an osteogenic sarcoma which had developed on a basis of radium ingestion many years ago enjoyed relief of chest symptoms (essentially chest pain and cough) for a period of two months. It is of interest that the cough was aggravated for the first five days after the P^{32}, after which there was a relief of symptoms. Another patient, with an unclassified sarcoma which had produced pulmonary metastases, was benefited by a combined course of P^{32} and HN_2 for a period of nine months, and she subsequently succumbed.

Five patients with pulmonary metastases from unknown primary neoplasm who received P^{32} therapy have all succumbed an average of five months after the isotope therapy. One patient (O.B.) enjoyed an excellent response with relief of all chest symptoms for a period of eight months, after which a rapid deterioration occurred and the patient died fourteen months after the P^{32} therapy. Another patient (F.B.) enjoyed relief of chest pain and a sense of well-being following the P^{32} therapy; this lasted three months and then she rapidly deteriorated. Two patients had no benefit whatsoever, and an additional one (F.S.) had some improvement in dyspnea and cough.

The Percentage Pick-up of P^{32} by Lung Tumors. Tables VI to XIII present the data designed to determine the relative pick-up of P^{32} by the neoplasm. It was obtained by placing a scintillation counter over a site which roentgenographically appeared to be the location of a given tumor. These data are presented as the percentage pick-up of P^{32} above the point of reference. For comparative values a corresponding site on the contralateral side of the chest was determined. The difference in each instance is presented as the difference of the percentage of counts above the corresponding points of reference. Attempts were made to present a running picture of the pick-up of the radioactive isotope as a function of time. This was not always possible because of the clinical situations.

The Percentage Pick-up of P^{32} by Primary Lung Tumors. Table VI presents the percentage pick-up of P^{32} by primary lung tumors. It is of interest that in each instance there was a greater pick-up of P^{32} at the site of the lung tumor over the corresponding site. The fluctuation, however, was very great, and varied from 117 per cent greater pick-up by the tumor site over a corresponding point on the contralateral chest wall to practically no apparent difference. The average pick-up above the point of reference by the tumor site at thirty minutes after injection was 40 per cent for the 8 patients in whom determinations were done. Twenty-four hours later, the percentage difference of pick-up by the tumor in the 4 patients in whom determinations had been made had decreased to 18.5 per cent. Forty-eight hours later, the percentage difference for 3 patients equalled 29 per cent. It is difficult to ascribe a reason for a decrease percentage-wise at twenty-four hours beyond that which was obtained for the forty-eight hour period. In one patient determinations were done one month later

Table VI

THE PERCENTAGE PICK-UP OF P^{32} BY LUNG TUMORS ABOVE THAT PICKED UP AT A POINT OF REFERENCE (PRETIBIAL REGION)

Primary Lung Tumor					
Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
M.B.	½ hr.	179	135	44	
	24 hr.	130	129	1	
	48 hr.	48	21	27	
J.C.	½ hr.	237	139	98	
A.G.	½ hr.	112	84	28	
	24 hr.	132	106	26	
	48 hr.	103	64	39	
	1 mo.	15	20	5	
M.K.	½ hr.	164	120	44	
Y.L.	½ hr.	181	112	69	
	24 hr.	83	46	37	
	48 hr.	14	3	11	
V.M.	½ hr.	191	120	71	
W.S.	½ hr.	100	86	14	
P.V.	½ hr.	249	132	117	
	24 hr.	137	127	10	

Table VII

THE PERCENTAGE PICK-UP OF P^{32} BY LUNG TUMORS ABOVE THAT PICKED UP AT A POINT OF REFERENCE (PRETIBIAL REGION)

Pulmonary Tumors Metastatic from Primary Breast Cancer					
Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
E.B.	½ hr.	221	95	126	
M.C.	½ hr.	—	—	—	
	24 hr.	256	77	179	
J.F.	½ hr.	58	39	19	
	7 da.	55	35	20	
I.L.	½ hr.	211	135	76	
	24 hr.	230	81	149	
E.R.	½ hr.	169	103	66	
	24 hr.	98	46	52	

and demonstrated an increase in the lung tissues of P^{32} over the point of reference. There was a greater pick-up by the contralateral side than by the site over the tumor.

It must be emphasized that these are crude data, necessitated by the extreme difficulties of localization of the exact site of the tumor by attempting to place the counter over a position determined by the chest roentgenogram. The geometry is such that a great amount of overlapping occurs, and it would be difficult to say with any degree of definiteness that the measurements were made directly over only tumor tissue by the techniques employed. The data, however, do prove that a given quantity of the radioactive phosphorus is concentrated by tumor tissue within the lungs.

The Pick-up of P^{32} by Pulmonary Tumors Metastatic from Primary Breast Cancer. These data are presented in Table VII and also reveal tremendous fluctuations in the different patients. The average concentrations for the 4 patients at a half-hour was 72 per cent greater at the site of the tumor than at the contralateral side. At twenty-four hours, an interesting observation consisted of the average concentration at the site of the tumor, for 3 patients, of 127 per cent. This is in sharp contrast to the 18.5 per cent observed at twenty-four hours for patients with primary lung cancer. It would indeed be difficult, on the basis of these data, to make the obvious conclusions that metastases from breast cancer concentrate far greater quantities of radioactive isotopes at twenty-four hours than the primary bronchogenic carcinoma. Other factors most likely play a role, which factors should be a subject for subsequent investigation.

The data for pulmonary tumors metastatic from cancer of the colon and rectum, from the female genitalia, and for a miscellaneous group reveal similar variations in the pick-up of the P^{32} by sites over tumor tissue and by corresponding sites over apparently normal lungs. The data are presented in Tables VIII, IX and X. Attempts to correlate the types of tumor, size of tumor, location of tumor, and other factors with these vagaries of P^{32} pick-up do not yield any apparent correlation. It accordingly remains enigmatic why such vast differences exist in the relevant pick-ups of P^{32} given to different patients, some with the same types of tumors. In others, the extent of the cancer within the pulmonary tissues appeared similar but marked differences of the pick-up occurred.

Pick-up by Lung Tissue after Administration of P^{32} Directly into the Heart. A study was undertaken to find if a polyethylene catheter introduced through the antebrachial vein directly into the right auricle, and thereby injecting the radioactive isotopes directly into the heart, could be more efficacious in concentrating the radioactive isotope in pulmonary tumors. The data of 1 patient so treated are presented in Table XI. During the third hour and the first three days there was a relevantly higher pick-up of the isotope over the tumor site than over the contralateral site; in the fourth and sixth days a reversal occurred and there was a greater pick-up by the contralateral side. The average pick-up, as determined by counting the isotope over various segments of the chest, did not reveal a significant pick-up of P^{32} by the pulmonary tissue over that which was administered by the intravenous route.

The Treatment of Lung Cancer by the Combined Use of P^{32} and Nitrogen Mustard. Table XII presents the effects of attempts to enhance the concentration of radioactive isotopes by a preliminary series of intravenous nitrogen mustard. Each of these patients received a course of radioactive phosphorus, and for a variable period afterwards received an average of 20 mg. of nitrogen mustard delivered intravenously, usually as a single dose but sometimes in divided doses of 10 mg. per day for two successive days. An average period of six days afterward another course of P^{32} was given, the same dose being used as initially. Counts were made to determine the pick-up

Table VIII

THE PERCENTAGE PICK-UP OF P^{32} BY LUNG TUMORS ABOVE THAT PICKED UP AT A POINT OF REFERENCE (PRETIBIAL REGION)

Pulmonary Tumors Metastatic from Cancer of Colon and Rectum

Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
J.B.	½ hr.	167	102	65	
	48 hr.	142	0.5	141.5	
	11 da.	34	7	27	
J.C.	½ hr.	83	163	−80	
	24 hr.	153	155	−2	
	8 da.	32	26	6	
T.R.	½ hr.	—	—	—	
	3 da.	204	79	125	
	5 da.	158	83	75	
C.R.	½ hr.	—	—	—	
	24 hr.	1390	216	1174	
S.K.	½ hr.	214	162	52	
	24 hr.	195	103	92	
	4 da.	171	83	88	
	7 da.	22	—	—	

Table IX

THE PERCENTAGE PICK-UP OF P^{32} BY LUNG TUMORS ABOVE THAT PICKED UP AT A POINT OF REFERENCE (PRETIBIAL REGION)

Pulmonary Tumors Metastatic from Primary Neoplasms of The Female Genitalia

Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
L.M.	½ hr.	—	—	—	
	2 hr.	130	153	−23	
	7 da.	99	0	0	
A.S.	½ hr.	—	—	—	
	2 da.	277	178	99	
F.M.	½ hr.	148	113	35	
	24 hr.	140	85	55	
	48 hr.	94	69	25	
T.D.	½ hr.	139	148	−9	
	24 hr.	36	13	23	
R.D.	½ hr.	—	—	—	
	2 da.	81	55	26	
	9 da.	191	18	173	
E.G.	½ hr.	329	356	−27	
	24 hr.	173	180	−7	

TABLE X

THE PERCENTAGE PICK-UP OF P^{32} BY LUNG TUMORS ABOVE THAT PICKED UP AT A POINT OF REFERENCE (PRETIBIAL REGION)

Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
Miscellaneous					
Genitourinary System					
Kidneys					
M.H.	½ hr.	61	162	−101	
	24 hr.	138	137	1	
Testicle					
D.P.	½ hr.	257	228	29	
	24 hr.	120	400	−280	
Sarcomas					
Fibrosarcoma					
S.A.	½ hr.	66	63	3	
	24 hr.	77	55	22	
	3 da.	102	52	50	
Unclassified Sarcomas					
M.H.	½ hr.	89	93	−4	
	24 hr.	100	110	−10	
	13 da.	1	33	−32	
O.B.	½ hr.	251	76	175	
	24 hr.	108	41	67	
F.B.	½ hr.	154	154	0	
	1 wk.	90	103	13	
Lymphomas					
N.R.	½ hr.	1	—	1	
H.vH.	½ hr.	75	90	15	
O.I.	½ hr.	277	128	149	
	4 da.	108	45	63	
	1 mo.	13	—	—	
H.G.	½ hr.	181	104	77	
	24 hr.	200	174	26	
Melanoma					
L.G.	½ hr.	250	136	114	
	24 hr.	155	48	107	
Pancreas					
L.P.	1 da.	86	61	25	
	2 da.	74	41	33	
H.K.	½ hr.	161	181	−20	
	24 hr.	129	113	16	
Esophagus					
N.C.	½ hr.	65	236	−171	

TABLE XI

THE PICK-UP OF P^{32} BY LUNG TISSUE AFTER ADMINISTERING THE P^{32} DIRECTLY INTO THE HEART

Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
E.B.	½ hr.	—	—	—	No significant difference from the pick-up of P^{32} by lung after intravenous administration
	3 hr.	178	130	48	
	24 hr.	247	147	100	
	3 da.	160	77	83	
	4 da.	135	168	−33	
	6 da.	60	63	−3	

TABLE XII

THE EFFECTS OF NITROGEN MUSTARD ON INFLUENCING THE CONCENTRATION OF P^{32} BY LUNG TUMORS

Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
J.F.	½ hr.	58	39	19	
(Before HN_2)	7 da.	55	35	20	
	½ hr.	70	64	6	
(After HN_2)	7 da.	46	39	7	
J.B.	½ hr.	167	102	65	
	48 hr.	142	0.5	141.5	
(Before HN_2)	11 da.	34	7	27	
	½ hr.	156	127	29	
(After HN_2)	48 hr.	130	30	100	
P.S.	½ hr.	128	151	13	
(Before HN_2)	24 hr.	150	130	20	
	½ hr.	117	80	37	
(After HN_2)	24 hr.	120	125	−5	
F.M.	½ hr.	148	113	35	
	24 hr.	140	85	55	
(Before HN_2)	48 hr.	94	69	25	
	½ hr.	140	110	30	
	24 hr.	163	162	1	
(After HN_2)	48 hr.	105	78	27	
A.G.	½ hr.	112	84	28	
	24 hr.	132	106	26	
	48 hr.	103	64	39	
(Before HN_2)	2 mo.	15	20	−5	
	½ hr.	351	206	145	
	24 hr.	160	155	5	
(After HN_2)	48 hr.	90	74	16	

Table XII—*Continued*

Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
I.T.	½ hr.	183	127	56	
(Before HN_2)	24 hr.	186	160	26	
	½ hr.	100	86	14	
(After HN_2)	24 hr.	62	76	−14	
F.L.	½ hr.	181	112	69	
	24 hr.	83	46	37	
(Before HN_2)	48 hr.	14	3	11	
	½ hr.	125	73	52	
(After HN_2)	24 hr.	52	43	9	
H.G.	½ hr.	181	104	77	
(Before HN_2)	24 hr.	200	174	26	
	½ hr.	337	233	104	
(After HN_2)	4 hr.	326	227	99	
M.H.	½ hr.	89	93	−4	
	24 hr.	100	110	−10	
(Before HN_2)	13 da.	1	33	−32	
	½ hr.	100	90	10	
	24 hr.	94	92	2	
(After HN_2)	12 da.	5	24	−19	

before and after the nitrogen mustard regimen, and these data are presented in Table XII. No significant enhancement of the concentration of P^{32} by a preliminary course of nitrogen mustard occurred. In several patients a smaller concentration of the isotope was observed after the course of nitrogen mustard than occurred preceding its use. The fluctuation of the data is so great that definite conclusions cannot be made relative to any effects of the HN_2 in influencing the pick-up of the P^{32}.

The Concentration of P^{32} Administered Intra-arterially. The effects of radioactive phosphorus introduced into a polyethylene catheter which had been threaded through the femoral artery, through the aorta, up to the thoracic aorta in the hope that the administered isotope might be carried via the bronchial arteries directly into the pulmonary tissues, and possibly more specifically into the tumor tissue, are presented in Table XIII. No great difference of concentration of P^{32} by the tumor over that which occurred when the isotope was delivered intravenously was noted.

DISCUSSION

The data herein presented indicate that the use of radioactive phosphorus as a means of treating pulmonary cancer, either primary or metastatic, is limited only to the alleviation of certain symptoms in patients who are not too metabolically depleted. In only 1 case is there any suggested evidence that prolongation of life may have been obtained by this modality. In those patients who enjoyed some palliation, it is difficult to state how much the irradiation contributed to the palliation. It is known that these people who are critically ill, and craving any type of assistance,

TABLE XIII

THE PICK-UP OF P^{32} BY LUNG TISSUE AFTER ADMINISTERING THE P^{32} INTRA-ARTERIALLY

Patient	Time after Injection	Percentage Pick-up above Point of Reference	Percentage Pick-up by Contralateral Side	Difference	Remarks
T.R.	½ hr.	—	—	—	
	3 da.	204	79	125	
	5 da.	158	83	75	
S.K.	½ hr.	—	—	—	
	24 hr.	167	67	100	
	2 da.	304	90	214	
A.S.	½ hr.	145	110	35	
	2 da.	277	178	99	
L.P.	½ hr.	—	—	—	
	1 da.	86	61	25	
	2 da.	74	41	33	

might be psychologically benefited by any treatment modality. It is impossible to state with any degree of conviction that the irradiation *per se* was instrumental in producing palliation, although palliation was obtained in a significant number of patients who were treated by this modality. Attempts to measure the uptake of the isotope by placing a scintillation counter over various aspects of the chest wall revealed that a measurable uptake of the isotope occurs within the tumor. In some instances the concentration of the isotope by the tumor appeared greater than in corresponding segments of lung tissue, whereas in others the lung tissue apparently concentrated a greater quantity than did the tumor. The marked variance which occurred both in a group of patients with a given type of tumor and in those with various tumor types did not fit into any ascertainable pattern by which a distribution curve could be plotted. The concentration of the isotope within the lung depends upon numerous factors which include the circulation to the lung, the amount of damage to the tumor-containing lung (such as the bronchiectasis, emphysema, etc.), the compromise of circulation to either the lung or the tumor, to mention a few. Attempts to correlate the various factors in this study were not rewarding and no correlation could be observed to account for the marked fluctuation in the concentration of radioactive isotopes by the technique herein employed. It is realized that the measurement technique is crude. It is impossible to place a counting tube over a given site and say that that site definitely represents tumor tissue only and to compare that with another portion of the lung which is believed to represent apparently normal lung tissue. The geometry precludes accurate measurement of this type. All overlying tissue which likewise contains varying amounts of P^{32} also contributes to the measurement of the isotope, especially superficial tissues, as shown by Marinelli. Although it would have been more exact to have placed a counter tube at a further distance from the chest wall by the use of a collimated tube of lead, nevertheless the necessity of measuring the beta rays required as short a distance as possible. Furthermore, exact directional efficiency was not required here since the exact tissue being measured could not be precisely determined.

Efforts to compare the quantity of isotope within tumor tissue directly, by dry-

ashing the material and comparing that with a given weight of normal lung tissue, were disappointing because of the differences of density between tumor and lung tissue. Attempts to equate the pick-up on a weight basis resulted always in a much greater pick-up of the isotope by the greater volume of lung tissue.

Efforts to enhance the concentration of the radioactive phosphorus by introducing it directly into the heart by means of a catheter threaded into the right auricle, or by introducing it directly into the aorta, apparently failed to produce a higher concentration of isotope in the tumor than did the simple intravenous method of administration.

Attempts to see if a preliminary course of nitrogen mustard might enhance the pick-up of radioactive phosphorus revealed that no such enhancement occurred. However, the patients who were treated by this regimen did fare better, and it is accordingly recommended that patients who are treated with a course of nitrogen mustard to control symptoms which are the result of an inoperable pulmonary cancer be given a course of radioactive phosphorus subsequent to the course of nitrogen mustard. In none of the patients studied in this series did any severe hematopoietic depression occur from the dosages used. However, when the P^{32} was given first, then followed by a course of nitrogen mustard which in turn was followed by another course of P^{32}, hematopoietic depression did occur.

Complications with this regimen are few, and no serious hematopoietic depression occurred in a patient who did not have a severe anemia or leukopenia, the result of metastasis to the bone marrow.

SUMMARY AND CONCLUSIONS

1. Radiophosphorus apparently exerted no beneficial influence on increasing the life span in patients with pulmonary neoplasms, either primary or metastatic.

2. An alleviation of troublesome symptoms due to the lung cancer occurred in a significant number of patients treated by an average dose of 10 mc of P^{32}.

3. Measurements of the concentration of radiophosphorus in various regions of the chest cavity (including the lung tumor) revealed a significant pick-up of the P^{32} by the tumor in most instances. It was not possible, by the techniques used, to determine accurately the actual pick-up of the P^{32} by the tumor and compare the differential pick-up ratio with other segments of the lungs.

4. The pick-up of P^{32} by the neoplasm and the normal lung tissues varied at different time intervals after the initial injection. The cause and significance of these fluctuations remain enigmatic.

5. Primary lung tumors and neoplasms metastatic from primary breast cancer apparently responded best to the intravenous administration of P^{32} therapy. Metastases from primary neoplasm of the uterus, ovaries, rectum and colon did not respond to this form of therapy.

6. Attempts to enhance the concentration of P^{32} in pulmonary neoplasms by administering the isotope intracardially, intra-arterially or subsequent to a course of nitrogen mustard were unsuccessful.

7. No serious untoward reactions occurred in this series of patients as the result of P^{32} therapy. Hematopoietic depression was usually slight.

8. The intravenous administration of P^{32} produces a definite but limited relief of troublesome symptoms due to pulmonary cancer.

139 East 36th Street
New York, New York

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INTERSTITIAL IMPLANTATION IN THE TREATMENT OF PRIMARY BRONCHOGENIC CARCINOMA*

By ULRICH K. HENSCHKE
NEW YORK, NEW YORK

APPROXIMATELY one-third (2,075 of 6,123 patients or 34 per cent according to our review of the literature[3]) of all patients with primary bronchogenic carcinoma are operated on with the intent of carrying out a resection. In nearly half of these (900 of 2,075 patients or 43 per cent), however, at exploration the tumor is found to be too far advanced for excision. At present in most hospitals, the chest is then closed. And while one may find consolation in the thought that the patient was given every chance, and that the extent of the disease and in some cases the diagnosis was established, the fact remains that a major operation with its concomitant morbidity, mortality, strain, and expense for patient and family was carried out in vain.

A possible way to make the best of this unfortunate situation is to use interstitial implantation with radioactive sources at the time of thoracotomy. Interstitial implantation has shown its superiority over external radiation therapy in many tumors, especially of the head and neck, some of which are comparable in biologic characteristics to primary lung cancer. Because of the technical difficulties of implantation and the problems of keeping a large supply of radon seeds on hand, interstitial implantation at thoracotomy as the principal method of treatment for lung carcinoma had been used only at a few large centers which owned a radon plant.[1,2] Through artificial radioisotopes, however, suitable radioactive sources for implantation at thoracotomy can be made readily available and interstitial implantation of lung cancer therefore deserves another look.

Table I summarizes the experience with interstitial implantation at thoracotomy at the Memorial Center.* The 1941–1955 Memorial Center cases have been reviewed in detail in a recent paper by Cliffton, Henschke, and Selby.[3]† If the operator has proper training and experience, interstitial implantation at thoracotomy is not a hazardous procedure and no serious complications have been encountered. A much higher tumor dose can be delivered than with external radiation therapy; tumor doses up to 35,000 r have been tolerated. In most cases, interstitial implantation can substitute for a postoperative course of external radiation therapy.

Of special interest for the evaluation of interstitial therapy are the 119 patients with primary carcinoma of the lung treated from 1941–1955, in whom interstitial implantation at thoracotomy was carried out but no resection was performed. These cases are a relatively uniform group, since they contain no early cases (these would have been resected at thoracotomy) and no late cases (these would not have been explored). Supplementary external radiation therapy was used in most cases in this 1941–1955 group in contrast to the 1956 and 1957 cases, where supplementary external irradiation was used only occasionally.

Table II gives the average and median survival time after thoracotomy in this group of 119 cases, as well as the 3 longest survival times. The large unclassified group contains the cases in which the diagnosis of malignant lung tumor was made by aspira-

* These series include all patients of the Thoracic Service (Chairman, Dr. Watson) as well as all private patients of Dr. Watson, Dr. Pool, Dr. Cahan, Dr. Cliffton, Dr. Conte, Dr. Goodner, and Dr. Luomanen.

† Since this paper was written, 11 more patients were found who had primary carcinoma of the lung treated with interstitial implantation at thoracotomy in the years 1949–1955. Thus, the figures differ slightly from those of the previous paper.[3]

* Presented at the Thirty-ninth Annual Meeting of the American Radium Society, Quebec City, Quebec, Canada, May 29–June 1, 1957.

TABLE I

PATIENTS TREATED AT THE MEMORIAL CENTER BY INTERSTITIAL IMPLANTATION AT THORACOTOMY

Year	Primary Lung Cancer		Other Lung Tumors		Total
	Without Resection	With Resection	Without Resection	With Resection	
1941	2	—	—	—	2
1947	—	1	—	—	1
1949	6	5	—	—	11
1950	16	3	—	—	19
1951	29	4	—	1	34
1952	16	4	—	—	20
1953	14	1	4	3	22
1954	18	1	2	1	22
1955	18	2	2	1	23
1956	35	5	7	—	47
1957	28	2	3	1	34
Total 1941–57	182	28	18	7	235

tion biopsy and in which the specimen was too small for further classification. The differences for the various histologic varieties are small. It is noteworthy how well patients with undifferentiated (oat cell) carcinoma fared with this type of treatment.

Significant results were obtained in superior sulcus (Pancoast) tumors of which 6 are included in Table II: 3 under the category of epidermoid, 2 under the category of unclassified carcinoma, and 1 under the category of adenocarcinoma. Median survival in this group is twenty-two months and average survival is better than twenty-four months. This superior sulcus tumor group also contains the only five year survivor in this group of 119 patients. It is remarkable that this patient had supraclavicular metastases proved by biopsy before exploration. He is still living, well, and free of pain. The other 5 patients with superior sulcus tumor survived four, four, fifteen, twenty-nine and thirty-five months, respectively; 4 had good relief from pain. Based on these results and on the response of 6 additional superior sulcus tumors which were interstitially implanted in 1956 and 1957, we feel that Binkley's[2] conclusion, that implantation is the treatment of choice in the Pancoast tumors, is justified.

Unfortunately, no data on the survival of patients with primary lung carcinoma, who were only explored and then treated with external roentgen therapy, are readily available. Studies are in progress to obtain suitable data for comparison. However, it was felt that the results with the patients treated with interstitial implantation at thoracotomy up to the end of 1955 were encouraging. Attempts have, therefore, been made to improve interstitial implantation at thoracotomy by better techniques and by the use of artificial radioisotopes.

Figure 1, *A* and *B* shows schematically

TABLE II

SURVIVAL DATA OF PATIENTS WITH PRIMARY LUNG CARCINOMA TREATED WITH INTERSTITIAL IMPLANTATION WITHOUT RESECTION AT THORACOTOMY 1941–1955

Histologic Classification	No. Patients	Survival in Months		Three Longest Survivals (months)
		Median	Average	
Epidermoid	55	7.7	9.8	63.0,*29.6, 24.7
Undifferentiated (oat cell)	27	6.7	9.1	53.4, 22.0, 20.6
Adeno and terminal-bronchiolar	10	6.9	10.4	28.3, 25.8, 11.7
Unclassified	27	7.4	11.7	35.1, 26.5, 24.5
All cases	119	7.4	10.2	63.0,*53.4, 35.1

* Living.

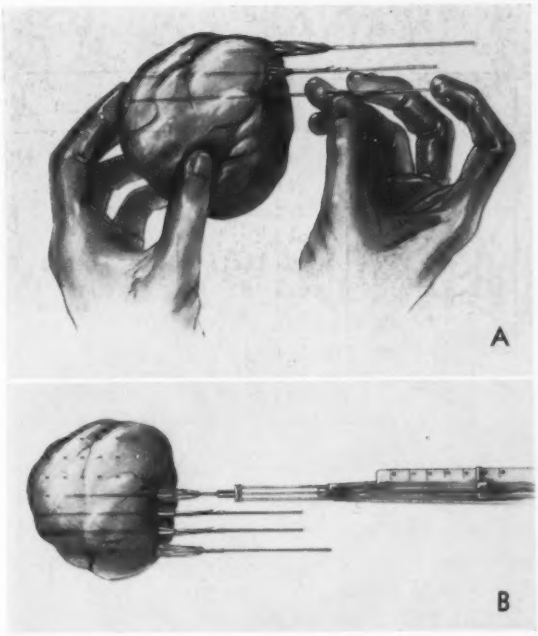

Fig. 1. Principle of new technique for permanent implantation. (*A*) Placing unloaded hollow needles in and around tumor. (*B*) Introducing radioisotope sources through special instrument with depth gauge, which is attached to each needle in turn.

a new implantation technique,[6] which has been used since the beginning of 1956 with radon as well as with Ir^{192} sources. Unloaded hollow needles, 15 cm. long, are first placed in and around the tumor. The implanted volume is determined by measuring with a ruler the separation of the needles and their outside length. The number of sources for the desired tumor dose is then determined. Next, a special instrument with a depth gauge is attached to each needle in turn. With it the desired number of radioisotope sources are introduced and properly spaced in the tissue. Figure 2, *A* and *B* shows the actual implantation of a bronchogenic carcinoma at thoracotomy.

Compared with the usual implantation technique with radon seeds, where each seed is introduced in an individual applicator, this technique offers the following advantages: (1) Implantation is more accurate, since the proper pattern and the correct depth of the needles can be ascertained prior to the introduction of the radioactive sources; (2) a number of sources can be introduced through one needle; (3) a planned dose can be accomplished more precisely; and (4) radiation exposure is reduced. These advantages are most valuable in large volume implants, which are the rule in interstitial implantation of primary bronchogenic carcinoma.

In the search for a more suitable radioactive source for permanent implantation, many artificial radioisotopes have been evaluated. Sources have been produced with radioactive gold (Au^{198}),[7,10] iridium (Ir^{192}),[6] tantalum (Ta^{182}),[4,11] chromium (Cr^{51}),[9] and mercury (Hg^{203}), but only Au^{198} and Ir^{192} were found worthwhile for clinical trials. In Table III their properties are compared with those of radon.

The gamma radiation from Au^{198} and Ir^{192} is energetic enough to avoid increased absorption in the bone. The dose rate for

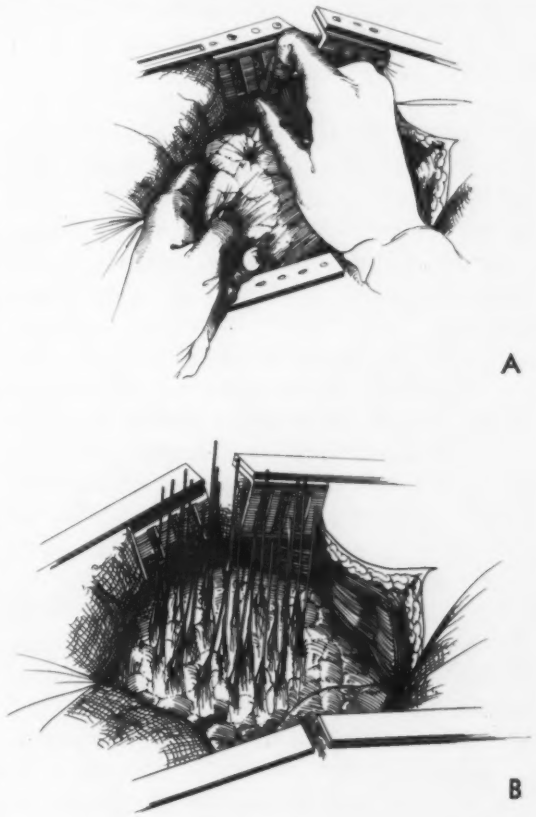

Fig. 2. Implantation of a lung tumor. (*A*) Placing empty hollow needles in and around the tumor. (*B*) All needles placed ready for introduction of radioactive sources.

TABLE III

COMPARISON OF RADIOISOTOPES USED FOR PERMANENT IMPLANTATION AT THORACOTOMY

	Radon	Gold	Iridium
Symbol	Rn^{222}	Au^{198}	Ir^{192}
Gamma lines	243–2198 kv.	411 kv.	136–613 kv.
Half-value layer in Pb (narrow beam)	7.9 mm.	2.7 mm.	2.3 mm.
Maximum beta energy	3,170 kv.	980 kv.	670 kv.
Cross-section	—	94 barns	750 barns
Diameter of source	0.8 mm.	0.8 mm.	0.35 mm.
Half-life (days)	3.8	2.7	74.5
Relative exposure in operating room	100	125	5
Relative exposure to hospital personnel for 11 day stay	100	105	10
Relative cost	100	50	2

these two artificial radioisotopes up to a distance of 6 cm. in tissue is the same as that with radon.[8] The same therapeutic effect up to this distance is, therefore, to be expected from comparable doses. At greater distances in tissues, the dose rates are lower with Au^{198} and Ir^{192} than with radon. This is perhaps a small advantage because the total body irradiation is lower.

Important in the practical use of the Au^{198} and of the Ir^{192} is the lower half-value in lead. This makes adequate protection for Au^{198} and Ir^{192} possible with relatively small lead containers which can be easily carried, while satisfactory lead containers for radon seeds are usually too heavy for convenient handling.

The lower maximum beta energy of the Au^{198} and Ir^{192} permits the use of thinner shields around the sources to filter out the beta particles. This, in combination with the high cross-section of the iridium to neutron capture, has made it possible to produce Ir^{192} sources which have a much smaller diameter than radon or Au^{198} seeds. While radon as well as Au^{198} sources (both 0.8 mm. diameter) have to be inserted through 17 gauge needles (outside diameter 1.45 mm.), the Ir^{192} presently used (0.35 mm. diameter) can be inserted through 21 gauge needles (outside diameter 0.8 mm.). These smaller needles are preferred because they cause less bleeding, less air leakage in the lung, and less trauma.

The longer half-life makes it possible to keep an adequate supply of sources on hand at any time. This is essential in the implantation of intrathoracic or intra-abdominal neoplasms, where one usually does not know before the operation whether resection, implantation, or no therapy at all is indicated. With the longer half-life of the Ir^{192}, the radiation exposure to the operating room personnel for the same total dose is 20 times lower than for radon, while for Au^{198} it is 1.25 times higher than for radon. This is important since radiation exposure in the operating room is the most difficult problem in radiation protection in the hospital. Also there is a considerable reduction of the radiation exposure for the hospital personnel outside of the operating room. The median time of stay in the hospital after thoracotomy with implantation for our patients is eleven days. During this time approximately 90 per cent of the radon dose, but less than 10 per cent of the Ir^{192} is delivered. The exposure to the hospital personnel is, therefore, reduced by a factor of 10. Higher exposure occurs, of course, to the family of a patient implanted with Ir^{192} as compared with radon after the patient returns home. However, these doses are low enough to be acceptable in view of the fact that this is a once-in-a-lifetime exposure.

Table III includes an attempt to make an approximate estimate of the relative cost of radon, Au^{198}, and Ir^{192} sources. This estimate takes into account the depreciation of the initial investment, the wages for personnel, the cost of material and irradia-

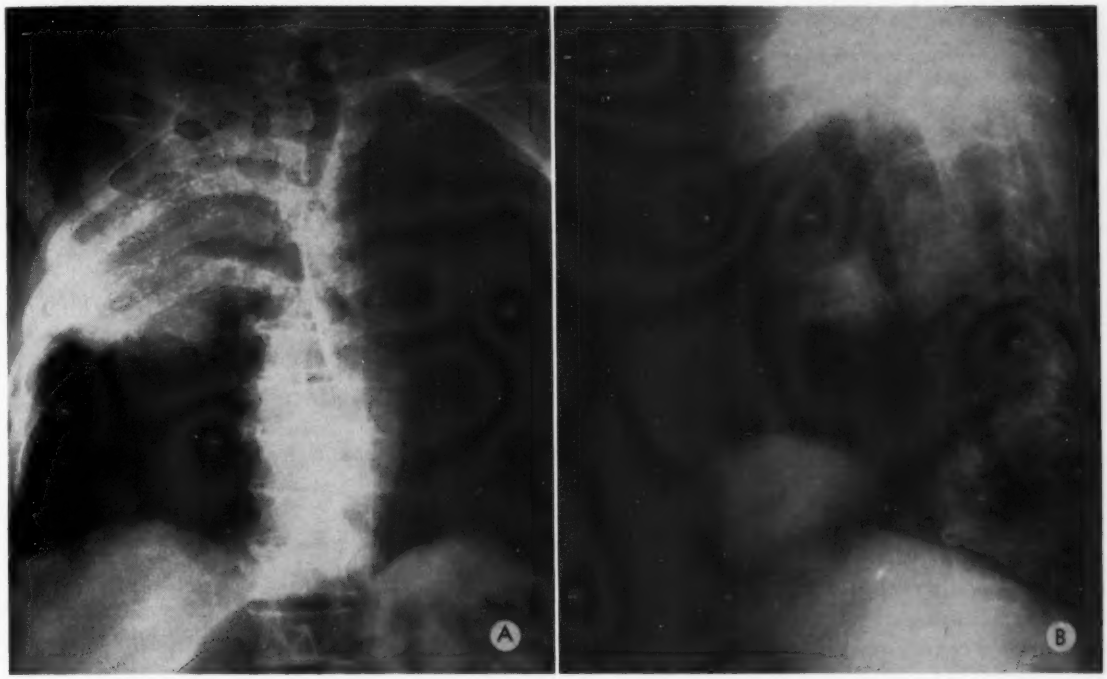

FIG. 3. (*A* and *B*) Permanent implantation with 284 Ir^{192} sources in a large bronchogenic carcinoma. Calculated total tumor dose 33,500 r.

tion, and the loss through unused sources. While this is not more than an educated guess, it was felt that it would be better to attempt it than to avoid the issue. If one considers that the seeds for an implant with 100 mc of radon, if commercially supplied, cost $450.00 in the United States, and that probably in half of the cases the radon seeds would not be used at thoracotomy because the lesion would be resectable, it becomes obvious that implantation of lung tumors with radon seeds is not economically feasible. Even with Au^{198} the costs are still prohibitive for most hospitals. Iridium^{192} brings the cost of an implant equivalent to 100 mc of radon to about $23.00, and all purchased sources can be used since they retain a suitable activity over a period of several weeks. Iridium^{192} sources would, therefore, make wider use of interstitial implantation at thoracotomy economically feasible.

The many advantages of Ir^{192} evident from the table have prompted a clinical trial in a greater percentage of patients since 1956. In 1956, 6 of the 47 implants were done with Ir^{192}; in 1957, Ir^{192} sources were used in 31 of the 34 implants. The remaining implants were done with radon.

Figure 3, A and B shows, as an example of the new implantation technique and of the use of Ir^{192} sources, a permanent implant with 284 Ir^{192} sources in a large carcinoma of the lung which occupied nearly the entire right upper lobe in a sixty-four year old man. The total activity of all sources was 23 mg. radium equivalent (or 35 mc Ir^{192} based on the value of 5.5 r per hour at 1 cm. distance for 1 mc of Ir^{192}), and the dose for total decay in the implanted volume was calculated from the Parker-Paterson tables to be 33,500 r. This was the most extensive implantation done in this series. Whether such large implants give worthwhile clinical results or whether implants should be reserved for smaller tumor masses must await further study.

It is too early to analyze the results of the 1956 and 1957 cases in which the new technique and Ir^{192} sources were employed. However, data on mortality and morbidity are available and are presented in Table IV.

TABLE IV

MORTALITY AND MORBIDITY OF PATIENTS WITH PRIMARY LUNG CARCINOMA WHO HAD EXPLORATORY THORACOTOMY BUT NO RESECTION 1941–1957

Type of Implantation	Years	No. Patients	Average		Mortality*	Morbidity (median day discharge)
			Seeds No.	mc		
Radon (old technique)	1941–1955	119	27	38.7	6/119=5.0%	11
Radon (new technique)	1956–1957	32	55	70.9	2/33 =6.1%	11
Ir^{192} (new technique)	1956–1957	31	127	223.1†	1/31 =3.2%	11

* Percentage of deaths in hospital (all occurred within thirty days after thoracotomy).
† Millicuries radon equivalent calculated on basis of total emitted gamma radiation. Corresponds to 12.9 mc Ir^{192}.

Only the cases of primary lung carcinoma are used which had exploration with implantation but which had no resection, since additional surgical procedures could dominate morbidity and mortality. In an attempt to get an objective measure for the immediate postoperative morbidity, the number of days in the hospital after thoracotomy was chosen.

As Table IV shows, there is no essential difference in immediate postoperative morbidity as measured by hospital stay among the 3 groups. The only marked side reaction in radon implantation after discharge has been a more or less severe esophagitis which usually lasts one to four weeks depending on the dose and location of the implantation. It necessitates a soft diet and clears up without specific treatment. This side reaction has been observed only to a very slight degree in large Ir^{192} implants and has not required any special attention or diet. This milder mucosal reaction in the esophagus is due to the lower dose rate with Ir^{192}.

The mortality was higher with the radon implantation in 1956 and 1957 than in the 1941–1955 period. This may be due to the greater number of seeds and millicuries used in the later period (average 1941–1955: 27 seeds and 38.7 mc; 1956–1957: 55 seeds and 70.9 mc). With some large radon implants in 1956 and 1957, the doses in the first postoperative days had reached several thousand roentgens, and this could conceivably complicate the postoperative recovery. However, in view of the small number of deaths, no definite conclusions can be drawn.

SUMMARY

While more work is necessary to establish the value and place of interstitial therapy in the treatment of lung cancer, our experience so far points to the following preliminary conclusions:

1. A much higher tumor dose can be delivered with less damage to normal tissues by interstitial implantation at the time of thoracotomy than by external radiation therapy.

2. Interstitial implantation at thoracotomy can be done with little risk and in most cases can substitute for a subsequent course of external radiation therapy.

3. Results of interstitial implantation in lung tumors are encouraging, especially in superior sulcus tumors.

4. Accuracy of interstitial implantation can be greatly improved by a technique in which unloaded hollow needles are placed in and around the tumor prior to the introduction of the radioactive sources.

5. Iridium^{192} appears to be a promising radioisotope for permanent interstitial implantation.

Memorial Center
444 East 68th Street
New York 21, New York

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THE PREOPERATIVE IRRADIATION OF BREAST CANCER WITH RADIOACTIVE COLLOIDAL GOLD (Au^{198})*

By MASAO OKUHARA, M.D., RYOICHI MONMA, M.D., KOJI ONODA, M.D., TOMOKICHI TAKEDA, AND TAKASHI HONDA
KANAZAWA, ISHIKAWA, JAPAN

THE present treatment of breast cancer consists of radical mastectomy with removal of the axillary lymph nodes as soon as the diagnosis is established, followed by postoperative irradiation with roentgen rays, radium, or a combination of both.

It is widely accepted that the survival rate of patients with breast cancer is increased by postoperative radiation therapy. Tsukamoto *et al.*[2] report that postoperative irradiation with radium inhibits recurrence in the operative scars and in the axillary lymph nodes, but has little effect upon the development of distant metastases. Nakaizumi *et al.*[1] state that recurrences and metastases occur less freqeuntly in fully irradiated cases than in partially irradiated cases. Survival rates can be improved to some extent by postoperative roentgen irradiation, but the development of metastases in parts beyond the scope of operation, such as the supraclavicular region, is difficult to suppress, and complete prevention of recurrences and metastases by radiation therapy is still far from being achieved.

In our clinic, two to three weeks prior to radical mastectomy the patient is given an intramammary injection of radioactive colloidal gold (Au^{198}). Telecobalt beam therapy is used for postoperative irradiation.

We have employed a colloidal suspension of radioactive gold (Au^{198}) in 8 cases of breast cancer (Table 1). In each case the diagnosis was established by histologic examination of biopsy specimens before the intramammary injection of radiogold.

METHOD

We inject 20 to 50 mc of radioactive colloidal gold (in a concentration of 1 mc per 1 cc.) into the cancerous breast, attempting to have as uniform a distribution of the colloidal gold in the breast as possible. Eight to ten sites of injection are usually selected in the peripheral part of the breast.

The radioactive gold, a product of Radiochemical Center in Amersham, England, is obtained in sterile colloidal suspension, stabilized with gelatin. The size of the colloidal particles in this suspension varies from 5 to 60 mμ. (the average size being 20 to 25 mμ.).

CLINICAL RESULTS

In our series, after injection of radiogold the temperature and pulse were normal with the exception of 1 case in which a slight fever continued for a few days. No marked blood changes were observed in any of the cases. In the injected breasts slight swelling and a local heavy feeling were noted. In 1 case in which there was a nonuniform distribution of the radiogold, pigmentation and erosion of the skin of the breast developed ten days after the injection. Studies with the Geiger-Müller counter performed every hour for forty-eight hours after injection failed to demonstrate radioactivity in the urine or blood specimens.

Radical mastectomy was performed two to three weeks after the intramammary injection of radiogold. The usual finding at the time of operation was a blackish-purple discoloration of the subcutaneous and fatty tissue in the breast and regional lymph nodes due to deposition of colloidal gold. Fragility of the tissues and friability of the blood vessels with a tendency to bleeding were also noted. In the cases in which the breast tumor had adhered to the thoracic wall, the discoloration had ex-

* From the Cancer Research Center, Kanazawa National Hospital, Kanazawa, Ishikawa, Japan.

Table I

Case	Age	Location of Tumor	Size of Tumor ($cm.^3$)	Histologic Diagnosis	Adhesion to Thoracic Wall	Metastases	Steinthal's Classification	Date of Au^{198} Injection	Injected Dose (mc)	Date of Operation
I. T.Ha.	52	Left upper lateral quadrant	5×5×2.5	Adenocarcinoma	(+)	(−)	III	March 22	20	April 7
II. K.M.	37	Left upper lateral quadrant	4×3×3	Adenocarcinoma	(−)	(−)	I	April 19	50	May 10
III. T.Ho.	39	Right upper lateral quadrant	3×3×1 2×2×0.5	Adenocarcinoma	(−)	(+) Axillary lymph nodes	II	April 19	50	May 10
IV. Y.S.	51	Right upper lateral quadrant	3×3×2	Adenocarcinoma	(+)	(+) Axillary lymph nodes	II	April 19	50	May 15
V. H.S.	45	Right upper medial quadrant	2×2×2.5	Carcinoma simplex	(−)	(−)	I	May 17	50	June 2
VI. M.T.	45	Right upper lateral quadrant	1×2×2	Adenocarcinoma	(−)	(−)	I	May 17	50	June 2
VII. Y.K.	39	Right upper medial quadrant	3×2×2.5	Adenocarcinoma	(−)	(−)	I	May 17	20	June 5
VIII. M.Y.	47	Right upper lateral quadrant	3×3×2	Adenocarcinoma	(−)	(−)	I	May 17	50	June 15

tended over the muscle layer under the breast. Discoloration of the axillary lymph nodes facilitated their detection at the time of the radical mastectomy. In 2 cases in which metastases had been found in the axillary lymph nodes, the outer layer of the lymph nodes was discolored with the peculiar hue of the colloidal gold encircling the gray-white focus of the metastatic carcinoma in the central part. Postoperative fever continued somewhat longer and healing of the operative wound was slightly retarded when compared to controls.

DOSAGE CALCULATION

Radiogold (Au^{198}) has a half life of 2.69 days and emits beta and gamma rays. The beta particles have a maximum energy of 0.97 mev., a maximum range in tissue of 3.8 mm., and an average path of 0.4 mm. The gamma rays have an energy of 0.411 mev.

(1) *Primary Breast Cancer.* Six or seven small pieces of tissue from different parts of an extirpated breast were obtained and the radioactivity for 1 gm. of tissue (μc/mg.) was measured with a Geiger-Müller counter. Assuming that the distribution of the radioactive gold in the breast at the time of measurement did not differ from the distribution immediately after the injection, the amount of deposited radioactive gold per 1 gm. of tissue was calculated. Although the distribution was not entirely uniform, the average amount of deposited gold in tissue (as shown in Table II) ranged from 103 μc/gm. to 253 μc/gm., when 50 mc had been injected, and from 86 μc/gm. to 244 μc/gm. when 20 mc had been injected. This average value was almost equal to the value obtained by dividing the injected dose (mc) by the volume of the breast. Therefore, it may be assumed that Au^{198} injected into the breast can distribute

TABLE II

Case	Injected Dose (mc)	Volume of Breast (cc.)	Injected Dose/Volume of Breast (μc/gm.)	Concentration of Au^{198} in Breast (μc/gm.)	Maximal Concentration of Au^{198} in Axillary Lymph Nodes (μc/gm.)	Ratio of Lymph Nodes in Which the Concentration of Au^{198} is More than 100 μc/gm.
I. T.Ha.	20	250	80	50–120 (86*)	310	1:4
II. K.M.	50	370	135	60–290 (123*)	1,000	7:15
III. T.Ho.	50	250	200	90–300 (212*)	1,330	9:11
IV. Y.S.	50	260	190	110–260 (185*)	550	4:11
V. H.S.	50	490	100	49–114 (103*)	731	9:12
VI. M.T.	50	220	226	142–445 (253*)	1,138	4:9
VII. Y.K.	20	80	240	183–305 (244*)	610	10:21
VIII. M.Y.	50	230	220	180–260 (206*)	624	5:22

* Average concentration.

almost uniformly throughout the breast if proper technical skill is employed at the time of injection.

While the beta radiation dose of 1 μc/gm. of Au^{198} to its complete decay amounts to 76 rep, in our series during the period between injection and operation it amounted to 75–76 rep, since the period ranged from 15.79 days to 25.8 days and the radioactivity at the time of operation decreased from 1.7 per cent to 0.1 per cent of that at the time of injection. Since the volume of the breast of an average-sized Japanese woman is considered to range from 250 cc. to 500 cc., the intramammary injection of 50 mc of Au^{198} resulted in a concentration of 100 μc/gm. to 200 μc/gm. in tissue (assuming uniform distribution) and gave a beta radiation dose of 7,500 to 15,000 rep during the period between injection and operation.

Assuming that the breast is a sphere with a radius of 4 to 5 cm., the gamma radiation to the central part of a breast injected with 50 mc Au^{198} can be calculated by the following formula:

$$\int_0^R 4\pi CKRe^{-\mu R}dR=\frac{4\pi CK}{\mu}(1-e^{-\mu R})$$

where R is the radius of a sphere-formed breast in centimeters, μ is the absorption coefficient of the gamma radiation emitted in a tissue equivalent medium (for Au^{198}, $\mu=0.034$ cm.$^{-1}$), C is the concentration of Au^{198} in mc/cc., and K is the number of gamma roentgens at 1 cm. from 1 mc of Au^{198} ($K=2.46$). This calculation gives 22.5 r_γ per hour where $R=4$ cm. and 13.7 r_γ per hour where $R=5$ cm. The average life of Au^{198} is calculated to be about 100 hours, therefore the total gamma radiation dose at the center of the breast amounts to from 1,370 r_γ to 2,250 r_γ during the period between injection and operation.

(2) *Metastatic Axillary Lymph Nodes.* Every lymph node was removed with the utmost care and the radioactivity in each was measured. It was assumed that the radiogold reached the lymph nodes shortly after injection, and the concentration was calculated on this basis. As shown in Table II, when 50 mc radiogold was injected, the maximum concentration in the lymph nodes ranged from 550 μc/gm. to 1,330 μc/gm., and with an injection of 20 mc, from 310 μc/gm. to 610 μc/gm. Approximately one-half of the removed lymph nodes in each case showed a concentration of more than 100 μc/gm. Also, in all of four lymph nodes in which the metastases of the cancer have been confirmed histologically, a concentration of more than 73.4 μc/gm. (from 73.4 μc/gm. to 500 μc/gm.) was found.

These data indicate that about one-half of the axillary lymph nodes can be irra-

diated with a beta radiation dose of more than 7,600 rep if the concentration is more than 100 μc/gm., and that a beta radiation dose of up to 38,000 rep can be given to lymph node metastases if the concentration is up to 500 μc/gm. and the cancer cells do not completely block the lymph nodes.

The gamma irradiation of each axillary lymph node results from the radiogold deposited in the lymph node itself, in the other lymph nodes, and in the breast tissues. The magnitude of the dose within the lymph node itself depends on its size and the concentration of Au^{198}. Since the average weight of the lymph nodes which were removed ranged from 0.25 gm. to 0.50 gm., we could consider the average size of the lymph nodes as equal to a sphere 0.4 cm. to 0.5 cm. in radius with regard to the volume. Calculating by the above described formula, the averaged-sized lymph node in which the concentration of Au^{198} is 100 μc/gm. is irradiated with a dose of 1.27 r_γ/hr. to 1.54 r_γ/hr., for a total dose of 127 r_γ to 154 r_γ. Assuming that the total amount (50 mc) of injected Au^{198} deposits in the center of the breast and that the distance from that center to the axillary lymph node is an average of 10 cm., the gamma radiation from the breast equals a dose rate of 1.3 r_γ/hr., that is, a total dose of 130 r_γ. The gamma radiation from neighboring lymph nodes can be disregarded because of the relatively long distance between them and the relatively small amount of radiogold in them. Thus, about one-half of the axillary lymph nodes can receive a gamma radiation dose of between 257 r_γ (127 r_γ+130 r_γ) and 284 r_γ (154 r_γ+130 r_γ).

HISTOLOGIC EXAMINATION AND AUTORADIOGRAPHY

With the aid of histologic sections and autoradiography, we studied the radiation effect of radiogold upon normal tissues of the breast and lymph nodes and upon cancer tissue, in relation to the distribution of the Au^{198} in tissue. In the histologic sections of the breast, we found multiple black particles, mostly phagocytosed by histiocytes which showed marked degeneration, such as clumping and disintegration of the nucleus and formation of vacuoles. These particles accumulated in the lymph passages around the blood vessels and mammary gland and were deposited in the stroma of the carcinoma. Around them there was a very pronounced inflammation, characterized by infiltration of lymphocytes, plasma cells, neutrophilic leukocytes and monocytes, proliferation of fibroblasts and histiocytes, appearence of giant cells, edema in connective tissue, coarseness of collagenous fibers, and severe endoarteritis or panarteritis with hemorrhage. Also, the epithelial elements (the epithelial cells of the mammary gland and of the excretory ducts) in the vicinity showed irregularity of arrangement, atrophy and degeneration. As the density of the distribution of these particles ran parallel to the intensity of the black areas in the autoradiogram of the same specimen and the radiation effects around these particles appeared as described above, we identified these particles as gold particles.

The cancer tissues around these particles were also injured, showing atrophy of the cells, clumping and destruction of the nuclei, formation of vacuoles and of giant cells (Fig. 1, 2, 3, 4 and 5). In some cases, in which the diagnosis of carcinoma had been established by histologic examination, the radiation effects of the Au^{198} were so

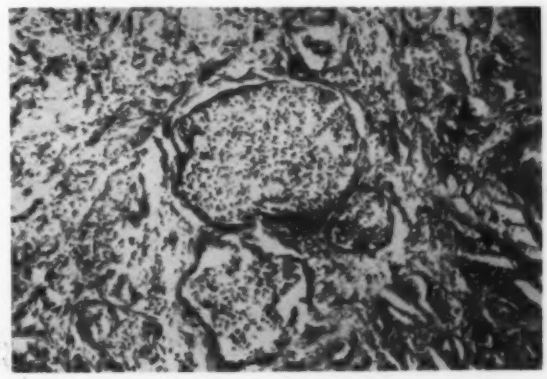

Fig. 1. Case VIII. Specimen taken from the breast before the injection of Au^{198}. Histologic diagnosis: adenocarcinoma.

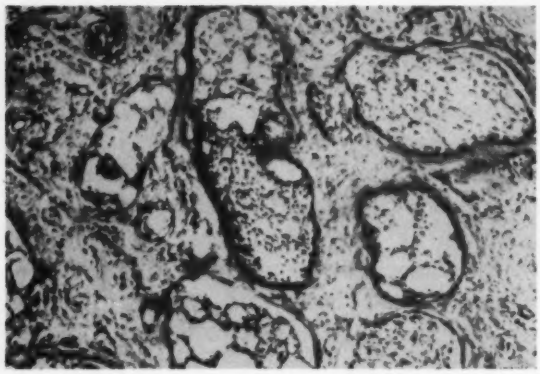

FIG. 2. Case VIII. Specimen taken from the breast nineteen days after the injection of Au^{198}. The atrophy of the carcinoma cells, the clumping and destruction of the nuclei, the formation of vacuoles and the irregularity of the arrangement are marked.

severe that the cancer tissue could hardly be demonstrated in the histologic specimens removed at the time of the radical operation.

In the lymph nodes the gold particles were mostly phagocytosed by sinus endothelial and reticulum cells, chiefly located in the subcapsular regions, in the hilus of the lymph nodes and along the reticuloendothelial pathways surrounding the follicles. They caused shrinking and destruction of lymph follicles, decrease of lymphocytes, relative increase of fibrous trabeculae of the medulla, hyperplasia of the sinus endothelial cells with infiltration of neutrophils and injury of the blood vessels leading to hemorrhage and arteritis. In

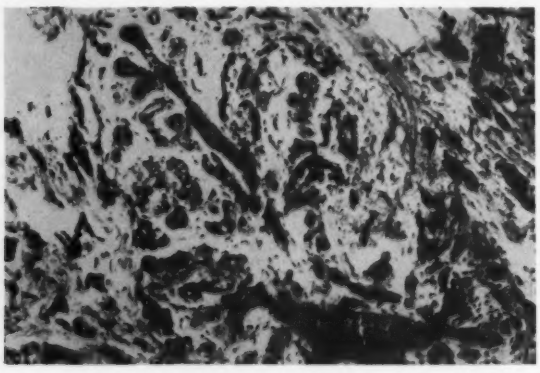

FIG. 3. Case V. Specimen taken from the breast before the injection of Au^{198}. Histologic diagnosis: carcinoma simplex.

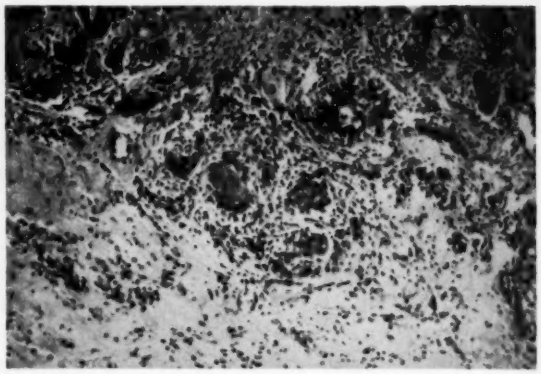

FIG. 4. Case V. Specimen taken from the breast nineteen days after the injection of Au^{198}. Cancer tissue shows atrophy, clumping of the nuclei, formation of vacuoles and giant cells, accompanied by infiltration of inflammatory cells.

some of the lymph nodes removed at a relatively long interval (about four weeks) after injection of radiogold, foci of complete necrosis and severe hemorrhages had been found.

The gold particles in the metastasized lymph nodes remained in the lymph spaces around the tumor mass and were not observed in the compact mass of cancer cells. The cancer cells in their vicinity were damaged, showing the evident radiation effects such as pyknosis, karyorrhexis, karyolysis and the formation of vacuoles. In the lymph nodes, too, these particles were identified as gold particles on the basis of the findings in autoradiography and in the histologic examinations.

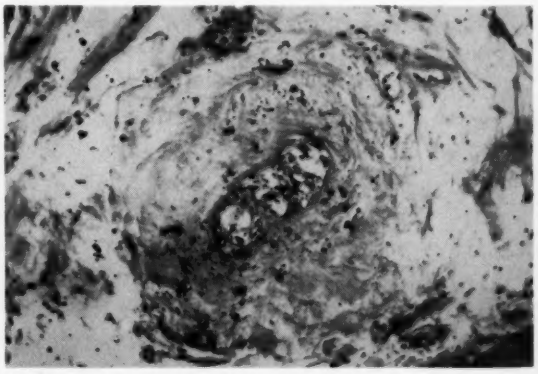

FIG. 5. Case IV. Specimen taken from the breast after the injection of Au^{198}. Multiple Au^{198} particles are shown around the degenerated cancer tissue where the fibrosis is very pronounced.

SUMMARY

Radioactive colloidal gold (Au^{198}) was used in 8 cases of breast cancer for the purpose of preoperative irradiation.

1. Colloidal gold (20 mc or 50 mc), injected into the breast, deposits in the subcutaneous and fatty tissue of the breast, resulting in a blackish-purple discoloration, and then reaches the axillary lymph nodes and discolors them in the same manner. This facilitates the detection of the lymph nodes at the time of radical mastectomy.

2. By the intramammary injection of 50 mc the dose delivered in the central part of the breast is 7,500 to 15,000 rep of beta radiation and 1,370 to 2,250 r_γ of gamma radiation. About one-half of the axillary lymph nodes receive a dose of more than 7,600 rep of beta radiation and a dose of 257 r_γ to 284 r_γ of gamma radiation, corresponding to the deposit of more than 100 μc/gm. of gold in them.

3. When the lymph nodes are not completely infiltrated with cancer cells, the radiogold can deposit in them and yield a dose up to 35,000 rep of beta radiation.

4. Gold particles in the breast, mostly phagocytosed by histiocytes, accumulate in lymph spaces around the blood vessels and mammary glands. The picture of inflammation is marked around the particles, and in these areas the epithelial elements are heavily injured and the blood vessels show severe arteritis.

5. Gold particles in the lymph nodes are present in lymph sinuses and are mostly phagocytosed by sinus endothelial and reticulum cells. The destruction of lymphatic tissues and lesions of blood vessels are noted.

6. Gold particles deposit in the connective tissue around the cancer in primary and metastatic foci and cause the damage of cancer cells in their vicinity.

7. This method of preoperative irradiation produces no marked side reaction and no significant complication. It can deliver sufficient radiation to the breast and axillary lymph nodes, showing typical radiation effects in histologic sections.

Masao Okuhara, M.D.
Cancer Research Center
Kanazawa, Ishikawa
Japan

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THE UPTAKE OF RADIOACTIVE RUBIDIUM (Rb^{86}) BY BREAST TUMORS*

By DAVID M. SKLAROFF, M.D.
PHILADELPHIA, PENNSYLVANIA

THE object of this investigation was to determine the possibility of differentiating between malignant and benign breast tumors by superficial counting over the tumors when compared with normal breast after the intravenous injection of a tracer dose of radioactive rubidium.

Low-Beer[2] first attempted to solve this problem by the use of radioactive phosphorus but was limited by the inherent limitations of P^{32} since it emits beta rays with a maximum range of 8 mm. in soft tissue. Benign inflammatory lesions caused an increase in the count rate and lesions deeper than 0.5 cm. from the skin and mucoid carcinoma did not produce any increase in count. In 1950, Selverstone *et al.*[5] noted that radioactive potassium (K^{42}) localized in high concentrations in a number of human cerebral tumors, the K^{42} emitting a gamma ray of high intensity (1.5 mev.). This was also confirmed by Moore *et al.*[3] but this group found that the short half-life (12.4 hours) limited its use to clinics near the source of supply. Five years later Baker *et al.*[1] studied the uptake of K^{42} by benign and maligant breast tumors. They concluded "Since 13 patients with malignant tumors had counting rates within the range of benign tumors, this procedure is not considered to be a diagnostic test."

At the meeting of the American Society of Clinical Investigation in Atlantic City on May 5, 1954, Tyer and Eldridge of Oak Ridge in a paper entitled "A Comparison of the Metabolism of Rb^{86} and K^{42} following Simultaneous Injection into Man" reported that rubidium may replace potassium in several biologic systems, and Ruffo and Lundaburn[4] showed that carcinoma of the esophagus, stomach, breast and uterus retained more rubidium than certain normal tissues when natural rubidium was administered parenterally. Zipser and Freedberg[6] demonstrated that more Rb^{86} was concentrated in primary brain tumors and in metastatic brain tumors of esophageal origin than normal brain tissue and that the dose of Rb^{86} adequate for localization studies in man is well below the range of toxicity.

MATERIAL AND METHODS

Patients with palpable mammary tumors admitted for surgery to the Albert Einstein Medical Center, Northern Division, were given a single tracer dose of 150 μc Rb^{86} intravenously. (The material used in this experiment was obtained from Abbott Laboratory, Oak Ridge, Tennessee.) Rb^{86} has a half-life of 19.5 days and emits 2 beta rays—1.822 mev. (80 per cent), 0.72 mev. (20 per cent) and 1 gamma ray—1.1 mev. The radioactivity over the skin covering the tumor, as well as over identical sites of the normal breast, was measured with a scintillation counter which had a 2 cm. lead shield and a 2 cm. thallium activated sodium iodide crystal closely applied to a photomultiplier tube (RCA No. 5819). A standard scaling unit was used.

Contact counts were made for five minutes. Various intervals between injection and counting have been used to determine the most effective interval for maximum differences. In the first few cases this was carried out for seventy-two hours. However, it was found that the peak uptake usually occurred during the first two hours. The test was usually discontinued after this time. The specimens of breast tissue after operation were sliced and separated macroscopically into malignant and nonmalig-

* From the Department of Radiology, Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania. This work was aided by A.E.C. Contract No. AT (30-1) 1796.

nant blocks and each was assayed for radioactivity. The samples were weighed and placed in a desiccator. When the daily weight failed to change, the tissue was placed in a well scintillation counter and the activity per milligram was determined.

Some difficulty was encountered in getting sufficient material since very often patients were admitted late in the afternoon of the day preceding surgery and time did not permit the performance of this examination. In several instances we were able to administer the tracer dose only preoperatively in the operating room and eliminated the external counting, but were able to obtain fragments of tissue specimens for counting. When the frozen section did not reveal any evidence of carcinoma, additional normal tissue was not removed and in these instances we were unable to make a comparison in uptake.

OBSERVATIONS

Thirty-six patients with mammary tumors were studied: 24 with malignant tumors and 12 with benign tumors—all histologically verified. Table I gives a classification of the malignant tumors and Table II of the benign tumors.

The percentage counting rate over the tumor, defined by the counting rate over tumor/the counting rate over the identical site of the normal breast ×100 was determined for the maximum uptake of each tumor.

Graph 1 represents a scattergram of the percentage counting rate of the benign and malignant tumors. Only 6 of the malignant tumors had a percentage uptake greater than 20 per cent and no breast containing a benign tumor had a counting rate over 20 per cent. However, the counting rate of the majority of the malignant tumors fell in the same range as that of the benign tumors.

The time of maximum uptake varied considerably, the peaks occurring between fifteen minutes and one hundred and twenty minutes.

Specimens for radioactivity assay work were obtained in 23 cases—4 benign and 19 malignant. The results of measurements of Rb^{86} concentrations in weighed samples of various excised tissue are given in Table III. Column 3 and 4 contain the specific activities per gram of normal and tumor tissue, respectively. These activities are valid for the day of operation, usually a day after injection of the radioisotope. The activities of the different tumors, as percentage of these over the normal tissue, *i.e.*, column 4 divided by column 3 ×100 are given in column 5. These are the percentages obtained in *in vitro* measurements.

In the 24 malignant cases studied, the concentrations of the radioisotope in normal tissue varied from 14 to 1,100 counts/gram, *i.e.*, by a factor of 80. The corresponding variation in the activities of the malignant tumor tissues was from 137 to 13,716 counts/gram, *i.e.*, by a factor of 100. Thus, as far as variation in the power of concentration of rubidium is concerned, there was a difference between malignant cells and normal cells. On the average, malignant tissues concentrated about 10 times as much rubidium as the surrounding normal structures and therefore received on the average 10 times as much irradiation

Table I

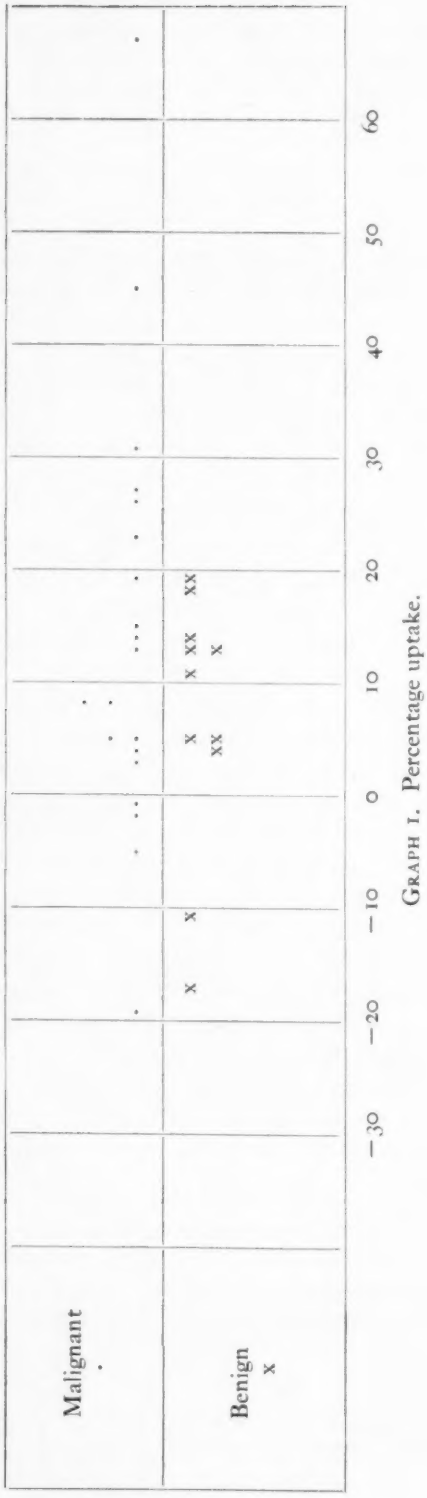
CLASSIFICATION OF MALIGNANT TUMORS

Scirrhous carcinoma	14
Large cell carcinoma	7
Adenocarcinoma	1
Anaplastic carcinoma	2
	24

Table II

CLASSIFICATION OF BENIGN TUMORS

Fibroadenoma	2
Cystic disease	6
Adenosis and intraductal papilloma	1
Lipoma	1
Gynecomastia	1
Ductal ectasia	1
	12



GRAPH I. Percentage uptake.

as the latter, while the nonmalignant tumors' average concentration was 4 times that of the surrounding normal tissue.

However, as shown in Table III, there were large variations in individual cases. From this table it can also be noted that there was no correlation between the degree of differentiation of the tumor and its uptake of radioactive rubidium.

DISCUSSION

The correlation of the ratios of activities per gram of tumor and normal tissue obtained in *in vitro* measurements, with those from superficial *in vivo* measurements is extremely difficult due to the presence of several complicating factors in each case. Although we were very careful in selecting the tissue for assay, it was practically impossible to be certain that the samples on which radioactive assay work was carried out contained exclusively either malignant or benign tumor or normal tissues and that there was no mixture in any case.

On the other hand, the counts registered by the counter placed on the skin surface is determined by counter geometry, the efficiency of the counter and the distribution of radioactive material within the tissues and the size of the tumor. In view of the presence of so many complicating factors, it is not surprising that a very rough agreement between the ratios obtained from the *in vivo* and *in vitro* measurements was not obtained.

More radioactive rubidium entered the carcinomatous breast than the normal when the labeled rubidium was injected intravenously. However, in the benign tumor, we also noted an increase in uptake but the average was much lower. It seems possible that more rapid metabolism of the malignant cells is responsible for this increase in uptake.

SUMMARY AND CONCLUSIONS

Radioactive rubidium (Rb^{86}) was administered intravenously in 24 patients with malignant tumors and 11 patients with benign tumors of the breast. Both

TABLE III

Patient	1 Diagnosis	2 Per Cent Difference External counting rate over tumor/ counting rate over normal breast ×100	3 Specific Activity counts/gram Normal	4 Specific Activity counts/gram Tumor	5 Activity of Tumor Percentage of normal tissue	Peak Uptake min.
C.B.	large cell anaplastic carcinoma	121	241.0	13,716.0	57	30
B.F.	cystic disease	119	1,406.0	2,423.0	1.7	90
R.H.	scirrhous carcinoma	102	not done	not done		30
M.C.	scirrhous carcinoma	114	23.0	703.0	30.6	30
S.D.	intraductal papilloma with adenosis	120	397.0	1,792.0	4.4	120
E.C.	lipoma	104	7.98	33.0	4.1	30
A.K.	large cell carcinoma	not done preoperatively	558.0	1,829.0	3.2	
T.R.	cystic disease	113	not done	not done		90
W.W.	gynecomastia	103	273.6	741.0	2.1	60
J.S.	fibroadenoma	113	not done	not done		60
S.W.	scirrhous carcinoma	103	451.4	1,146.0	2.5	30
F.W.	scirrhous carcinoma	98.8	not done	not done		30
A.S.	scirrhous ulcerating carcinoma	95.4	not done	not done		15
D.L.	scirrhous carcinoma	104	1,100.0	3,000.0	2.7	
E.A.	adenocarcinoma	107	65.0	232.0	3.4	
B.S.	large cell partly scirrhous carcinoma	114	not weighed	not weighed		90
G.R.	scirrhous carcinoma	no external counts	68.0	493.0	7.2	
L.D.	large cell carcinoma	144	147.0	1,106.0	7.5	
M.G.	scirrhous carcinoma	no uptake noted	14.0	459.0	32.7	60
E.F.	large cell carcinoma	120	100.0	137.0	1.37	90
E.L.	large cell carcinoma	not obtained	20.7	206.0	9.9	60
R.G.	infiltrating anaplastic carcinoma	115	47.0	148.0	3.0	60
M.L.	infiltrating carcinoma	104				30
M.S.	scirrhous carcinoma	107	46.0	283.0	6.1	30
M.K.	fibroadenoma	83.0	none	none		30
M.K.	cystic disease	104	none	857.0		30
C.J.	scirrhous carcinoma	127	24.0	137.0	5.2	30
B.H.	cystic disease	not obtained		34.0		
B.S.	cystic disease	114	not done	not done		30
R.T.	ductal ectasia	111	not done	not done		30
P.G.	large cell carcinoma	188	81.0	202.0	2.4	15
A.B.	scirrhous carcinoma	126	172.0	997.7	5.7	30
I.A.	scirrhous carcinoma	130	109.0	245.0	2.2	15
E.B.	large cell carcinoma	81.6	34.0	192.5	5.6	60
M.D.	scirrhous carcinoma	97.4	47.5	212.28	4.4	30
J.Z.	cystic disease	89.7	not done	not done		15

external *in vivo* counts and *in vitro* counts on the desiccation samples of tissue were performed. An average increase in uptake by malignant tumors of tagged rubidium was noticed both *in vivo* and *in vitro* but it was not sufficient to be of diagnostic value.

5500 Old York Road
Philadelphia 41, Pennsylvania

We are very grateful for the laboratory assistance of Miss Hettie Brenz.

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LIGHT BEAM TRIANGULATOR FOR MEASURING THYROID-COUNTER DISTANCES IN RADIOIODINE UPTAKE STUDIES*

By ARTHUR L. DUNN, PH.D., *and* WILLIAM G. BERAN, B.Sc.
OMAHA, NEBRASKA

IN COMPARATIVE external *in vivo* counting techniques such as thyroid uptake measurements, the geometric relationships must be accurately maintained and easily reproduced. The problem of keeping a constant distance from the counter to the patient's body or to the standard source has been handled in several ways. Some workers have preferred to use a metal or plastic rod of appropriate length; others have used a weighted chain. Several apparent disadvantages are presented by these methods. In this laboratory there has been constructed a device which eliminates these difficulties.

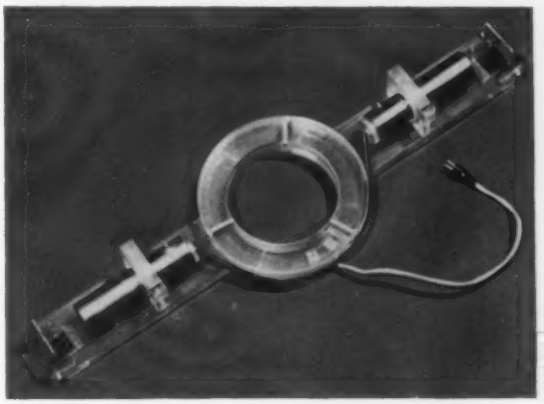

FIG. 1. Close-up view of light beam triangulator.

CONSTRUCTION

This device can be attached to any counter assembly and makes use of two light beams following a triangular path which, when so adjusted that their images superimpose, establish the counter-to-patient distance within a few millimeters. The illustrations are largely self-explanatory; no precise dimensions are given since each of the various makes of counters will require a somewhat different mounting arrangement. Figure 1 shows the triangulator detached from the counter. The light sources are contained in the metal cylinders and consist of 6.3 volt 0.25 ampere radio pilot lamps, power to light them being supplied by tapping in on the 6.3 volt filament source for the preamplifier. A switch is built into the preamplifier housing to turn the lamps off when not in use.

The metal cylinders are mounted on a piece of half-inch lucite plastic two and one-half inches wide and twenty-one inches long, shaped, as shown, to fit around the counter barrel. Collimation is accomplished by a convex-convex lens placed at the outer end of each cylinder. The lamp filaments are oriented so as to be in the horizontal plane. Their images are reflected by polished aluminum mirrors at the ends of the plastic frame and are arranged to be superimposed when the counter is at the desired distance from the patient's thyroid region. As is obvious, the greater the distance between the mirrors, the greater the precision of positioning.

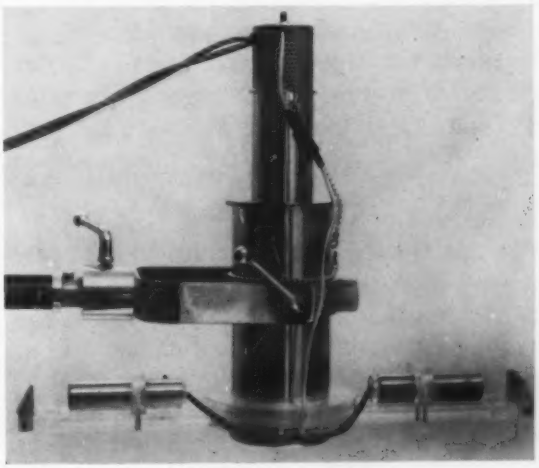

FIG. 2. Device mounted on counter.

* From the Radioisotope Service, Veterans Administration Hospital, Omaha, Nebraska.

Figure 2 is a close-up view of the triangulator in position on the counter, showing the plastic collar which positions the device against the end ring of the counter housing.

Figure 3 is an over-all view of the device showing the light beams superimposed on a patient's neck when the counter is at the correct distance.

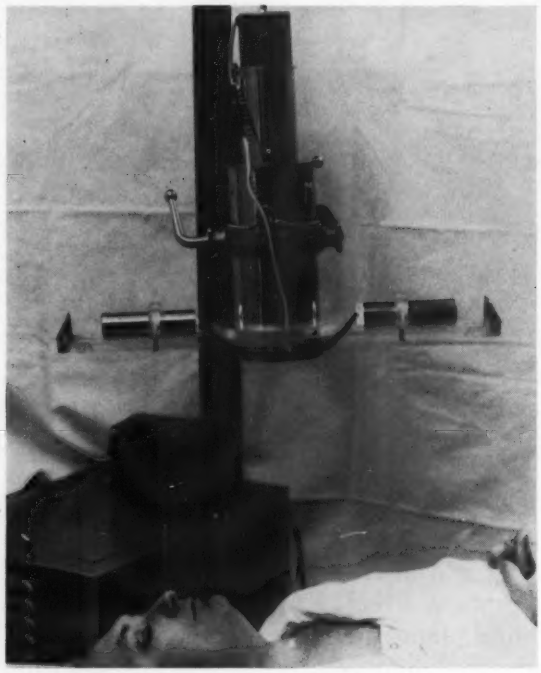

FIG. 3. Superimposed light beams on patient's thyroid area.

SUMMARY

A light beam triangulator has been constructed which allows for maintaining a constant counter-to-patient distance during thyroid radioiodine uptake studies without resorting to metal or plastic rods or lengths of chain.

The advantages of this method over former techniques used are:

1. The patient may be in a standing, sitting or supine position.
2. No protrusions from the counter are necessary.
3. Distance may be repeatedly checked throughout the procedure.
4. Resetting of mirrors for any counter-patient distance can be accomplished quickly and checked with a meter rule.
5. The cost is minimal.

Arthur L. Dunn, Ph.D.
Radioisotope Service
Veterans Administration Hospital
4101 Woolworth
Omaha 5, Nebraska

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COMPARISON OF THE UPTAKE OF RADIOACTIVE IODINATED HUMAN SERUM ALBUMIN BY LIVER TISSUE AND LIVER METASTASES*

REPORT OF FOUR HUMAN CASES

By DOUGLAS W. MacEWAN, M.D.
MONTREAL, QUEBEC, CANADA

STIRRETT, Yuhl and Libby with other co-workers[7,8,9] have reported a method to detect liver metastases using a radioactive technique. Human serum albumin, tagged with radioactive iodine was injected intravenously and external counting over the liver region was performed. Normal controls appeared to differ from patients with metastases in the liver and it was assumed that deviations from normal were due to selective uptake of radioactive material by the metastases. The differences were sufficiently marked that the technique seemed to offer a simple accurate method of detecting liver metastases. Madell, Kligerman, Quimby and Fertig,[4] however, found that the method is not reliable. The procedure was also found to be unreliable by Beierwaltes, Johnson and Solari.[2]

The technique developed by the original workers was used at the Montreal General Hospital to study 49 patients,[3] most of whom were from the Radiation Therapy Department of the hospital. Eighteen cases were adequately assessed by operation or postmortem examination, and no practical accuracy in detecting liver metastases was found as only 10 cases were correctly predicted. The reason for this report is that 4 of the patients died shortly after injection with radioactive human serum albumin and the livers which contained metastases were studied for radioactivity.

CASE MATERIAL

The details of the 4 patients who died of carcinomatosis shortly after injection with radioactive human serum albumin are given in Table 1.

The livers were removed from the bodies about an hour before the liver tissues were counted. The liver tissue considered normal was obtained as far removed from the metastases as possible, and away from the capsule and large blood vessels. The liver metastasis samples were taken from the central portion of the metastatic tumors. The border tissue between liver and liver metastases was 2 mm. thick, and was half liver and half metastasis. The tissues were dissected by hand, kept as free of blood as possible, and were prepared as an emulsion for counting.

The counting results for Case 1 were obtained by placing the samples at a distance from a scintillation assembly normally used for external counting. The results for the remaining cases were obtained by placing the samples immediately adjacent to a scintillation crystal. The samples in Case II could not be brought to the uniform weight and volume desired, but all the counting rates are expressed as counts per gram. The background count has been removed from the values in the table. All figures are based on counting totals of over 10,000. The similar counts of the tissues in each case suggest that there is no difference in the uptake of the liver or of the liver metastases.

DISCUSSION

Selective uptake of radioactive substances by certain tumors has been demonstrated as, for example, in the brain tumors of humans and mice.[1,5,6] The factors affecting concentration are the time elapsing after injection and the vascularity of the tumor. It is not known if such selective uptake occurs in liver tumors following intra-

* From the Department of Radiology, Montreal General Hospital, Montreal, Quebec, Canada.

TABLE I

Case	I	II	III	IV
Sex	male	male	female	female
Age	61	51	55	52
Primary Tumor	stomach	stomach	breast	breast
Time from Injection until Death (hr.)	44	23	14	11
Time from Death until Tissues Prepared (hr.)	7	24	8	7
Liver Weight (gm.)	1,840	1,900	1,490	3,500
Gross Appearance of Liver	many large metastases up to 4 cm. size	two metastases, right lobe 7 gm. left lobe 1 gm.	many metastases 0.5–5 cm.	¾ of liver replaced by metastases
External Counting Prediction	metastases	no metastases, done 7 mo. before	not done	not done
Sample Weights (gm.)				
liver	25.0	5.00	5.00	5.00
metastases	25.0	4.48	5.00	5.00
border tissue	25.0	4.61	5.00	5.00
Liver Counts per min./gm.	16	1,100	7,700	1,850
Metastases Counts per min./gm.	16	1,050	5,800	2,050
Border Tissue Counts per min./gm.	11	1,100	6,400	1,850

venous injection of radioactive iodinated human serum albumin. Madell and coworkers[4] counted at twenty-four and forty-eight hours after injection and noticed abnormal and differing counts, but these did not correspond to known sites of liver metastases or abdominal tumors. Yuhl with his group of workers[9] attempted to assess tissue samples by radioautographs, but the radioactivity was too low; and also the primary tumor did not acquire an unusual degree of radioactivity. No radioactive assays of liver biopsies and no detection of increased activity in liver metastases by probing for radioactivity have been reported. Phantom work has been discussed and performed by Yuhl *et al.*[9] and Madell *et al.*[4] For detection by external counting, metastatic tumors in the liver would have to be approximately 2 cm. in diameter and would have to contain two to three times as much radioactivity as the surrounding tissue.

The 4 cases presented in this paper suggest that there is no useful differential uptake between metastases of the liver and the liver parenchyma and that external counting methods to detect liver metastases using radioactive iodinated human serum albumin have no fundamental basis.

SUMMARY

Postmortem studies were made on 4 patients with liver metastases who had received radioactive iodinated human serum albumin intravenously shortly before death. No selective concentration of radioactive material by the liver or by the liver metastases could be demonstrated.

3534 University Street
Montreal 2, Quebec
Canada

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THE FATE OF I^{131} TAGGED ROSE BENGAL IN THE RAT*

By ANTONE G. JACOBSON, PH.D., *and* ROBERT L. BRENT, M.D., PH.D.
WASHINGTON, D.C.

THE use of the fluorescein dye, rose bengal, to determine the functional state of the liver was reported by Delprat[2] in 1923. He stated that the dye is eliminated entirely in the bile and at no time appears in the urine. The recent availability of rose bengal tagged with radioactive iodine (I^{131}) may greatly increase its use in determining the status of liver function,[1,5,7,8] in localizing liver abnormalities,[6] and as a test of bile duct patency.[3]

In the present investigation of the fate of I^{131} tagged rose bengal in the rat, it is proposed: 1. To establish the time relationships of liver uptake and excretion of rose bengal and to determine the amounts of radioactivity in other tissues. 2. To determine if I^{131} is dissociated from the rose bengal molecule *in vivo* by comparing thyroid uptake of radioactivity in rats injected with tagged rose bengal and rats injected with NaI^{131}. 3. To determine the amount and rate of excretion of I^{131} in the urine following intravenous administration of radioactive rose bengal and in the same animals determine the distribution of radioactivity in feces and tissues. 4. To study the distribution of radioactivity following administration of tagged rose bengal directly into the stomach.

EXPERIMENTS

1. Disposition of Radioactivity in Rat Tissues following Intravenous Injection of Rose Bengal (I^{131})

Material and Methods. Eighteen and eight-tenths microcuries of rose bengal were injected into a tail vein of each of eight female white rats. At various time intervals the rats were sacrificed, selected tissues and organs removed and weighed to the nearest tenth of a milligram, and digested in sodium hydroxide. The amount of radioactivity in each sample was measured with a DS-3, Nuclear, scintillation well-type counter.

Results. Radioactivity was concentrated in the liver and thyroid. Other tissues, including clotted blood, kidney, adrenal, ovary, spleen, lung, uterus, abdominal muscle, mesenteric fat, and lymph node, contained relatively small amounts of radioactivity per milligram of tissue (Fig. 1).

The liver contained a maximum amount of radioactive rose bengal approximately twenty-four minutes after injection (Fig. 2), and the amount then decreased sharply. The amount of radioactivity in the upper intestinal tract rose rapidly and was directly related to the amount of rose bengal excreted by the liver into the bile and then into the intestine.

2. Thyroid Uptake of Radioactivity following Intravenous Injection of Tagged Rose Bengal Compared to Thyroid Uptake following Intravenous Injection of NaI^{131}

The relatively large amount of radioactivity in thyroid tissue (Fig. 1) led one to suspect a dissociation of I^{131} from the rose bengal molecule *in vivo*. The amount of radioactivity in the thyroid considerably exceeded the amount that would be expected from accumulation of free iodide in the rose bengal solution at the time of injection. The manufacturer stated, on the basis of chemical and chromatographic determinations, that only a few tenths of 1 per cent of the iodine is unattached and in the form of iodide, and further, that storage for two to three weeks does not materially increase the free I^{131} content.[4] The present experiments show that forty-six and one-half hours after injection of 18.8 μc, 0.493 μc or 2.6 per cent of the total was in the

* From the Department of Biophysics, Walter Reed Army Institute of Research, Washington, D. C.

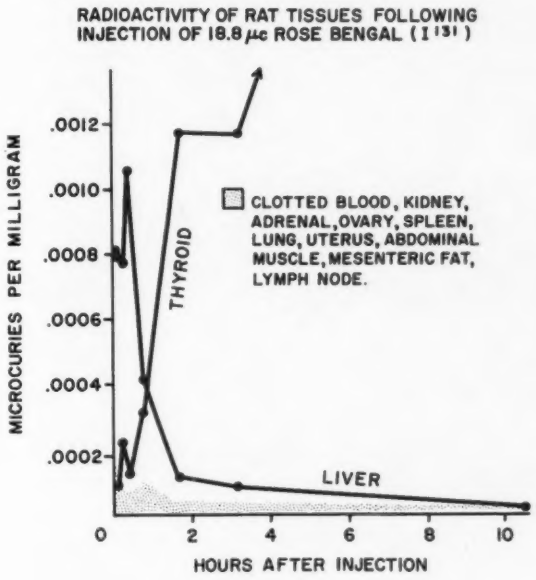

FIG. 1.

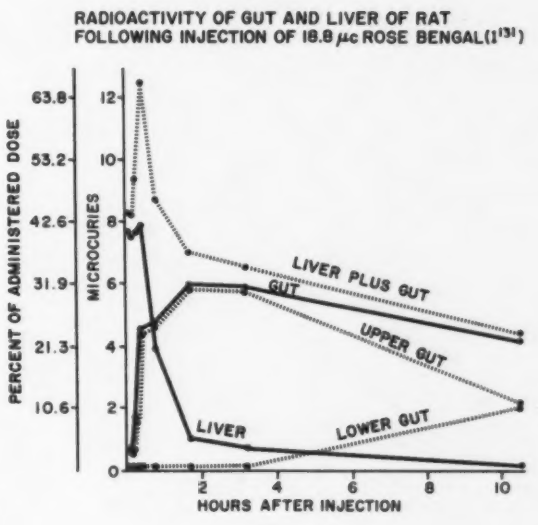

FIG. 2.

thyroid gland. Since the rat thyroid accumulates, according to past experiments in our laboratory, only 10 to 20 per cent of administered radioiodine, 13 to 26 per cent of the iodine in the rose bengal solution must, in this case, have been in the form of the free iodide in the body. Evidently a considerable amount of I^{131} is dissociated from the rose bengal molecule *in vivo*.

Further experimental evidence for this assertion was obtained. A rat administered a single intravenous injection of I^{131} tagged rose bengal may receive a small initial dose of free I^{131}, that is, the I^{131} free in the rose bengal solution at the time of injection, plus an additional chronic dose as the I^{131} is continuously dissociated from the rose bengal molecule *in vivo*. The pattern of thyroid uptake of I^{131} in an animal administered a single intravenous injection of rose bengal (I^{131}) should show the characteristics of chronic administration of I^{131} and would differ, therefore, from the pattern obtained from an animal given a single intravenous injection of NaI^{131}. The amount of I^{131} in the thyroid would be expected to decline more slowly in rats administered rose bengal (I^{131}) than in rats given NaI^{131}, and the maximum uptake should occur later. This comparison is made in the following experiment.

Material and Methods. The rate of uptake and excretion of iodine by the thyroid was measured by an external counting system consisting of a Nuclear, DS-1, external scintillation counter and a restricting rack to immobilize the animals. The counter was shielded from the animal except for a three-eighths inch hole in the protective lead of the counter superimposed over the region of the thyroid. The animal's position was adjusted until a maximum count was obtained. Two rats were injected intravenously with 50 μc of I^{131} tagged rose bengal and 2 were injected with 20 μc of NaI^{131}. The thyroid was counted several times daily for seven days.

Results. Comparison of the results for the two groups is facilitated by converting the figures obtained in counts per minute to fractions of maximum uptake for each animal by dividing counts per minute obtained at each time by maximum counts per minute obtained for that animal (Fig. 3).

The decline in the amount of I^{131} in the thyroids was less rapid in the rats that received the radioactive dye. This finding indicates a continuous dissociation of I^{131} from the rose bengal molecule in the rat's

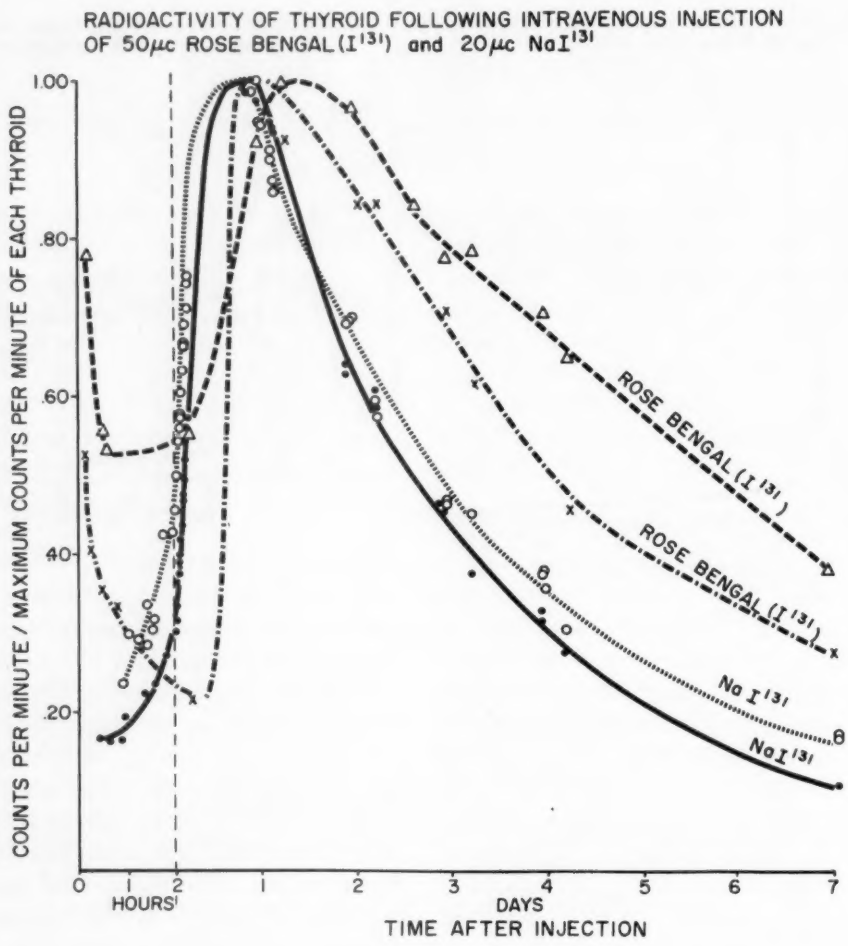

FIG. 3.

body. Although the maximum uptake did occur later in the rose bengal injected animals, this finding is not as significant as the multiple points that demonstrate a less rapid decline in radioactivity of the thyroids.

The high, but rapidly decreasing radioactivity of the thyroid region found immediately after injection of rose bengal (I^{131}) (Fig. 3) was due to circulation of the dye in the blood. The rapid decline in the radioactivity reflected clearance of the dye from the blood by the liver.

Taplin, Meredith, and Kade,[8] in contradiction to our findings in rats, state, "The I^{131} appears to be firmly integrated into the dye molecule, since only negligible amounts of radioactivity can be detected in thyroid tissue of rabbits 24 hours following intravenous injections of 30 microcuries of the radioactive dye." It was suspected that a difference in counting techniques may explain the disparity between our results and theirs. To test this, 40 μc of rose bengal (I^{131}) was administered to a rabbit. The animal was sacrificed twenty-four hours after injection; the thyroid was removed and digested in sodium hydroxide. The radioactivity in the thyroid was measured in a scintillation well-type counter. This thyroid contained 0.171 μc of I^{131} or 0.43 per cent of the administered dose. Assuming an uptake of 10 to 20 per cent of the available I^{131}, 2.1 to 4.3 per cent of the radioiodine in the administered rose bengal must have dissociated in the rabbit's body.

Evidence of dissociation of I^{131} from the rose bengal molecule *in vivo* in man is provided by a case where rose bengal was administered to a child with biliary atresia as a test for bile duct patency.[3] One week after the intravenous infusion of the radioactive dye, 7.8 per cent of the administered radioactivity was concentrated in the thyroid gland. Furthermore, daily twenty-four hour urine samples contained exponentially decreasing amounts of I^{131}. Both of these findings demonstrate a continuous dissociation of the rose bengal.

Should a hepatoscan, requiring up to 250 μc of radioiodine tagged rose bengal,[6] be performed on a patient with a partially or completely obstructed biliary system, some thought should be given to the radiation dose to the thyroid.

3. Excretion of I^{131} in the Urine following Intravenous Administration of Rose Bengal (I^{131})

Since the thyroid of the rat accumulated I^{131} following administration of tagged rose bengal, it was expected that I^{131} would be excreted in the urine. The amount and excretion rate of radioactivity in the urine was determined in the following experiment.

Material and Methods. A female white rat was anesthetized with sodium nembutal and 18.8 μc of rose bengal (I^{131}) was injected into a tail vein. A suprapubic tube was inserted and the urethra was closed off by tying a loop tightly around its external orifice. Urine was collected for two days in fractionated samples and the amount of radioactivity was measured with a scintillation well-type counter. The animal was sacrificed forty-six and one-half hours after injection, and selected tissues were dissected out and digested in sodium hydroxide. The remaining carcass was also digested. All feces evacuated during the experiment were collected and dissolved. The volume of each sample was determined and the amount of radioactivity in 2 ml. aliquots measured. The total amount of radioactivity in each sample was calculated using these figures.

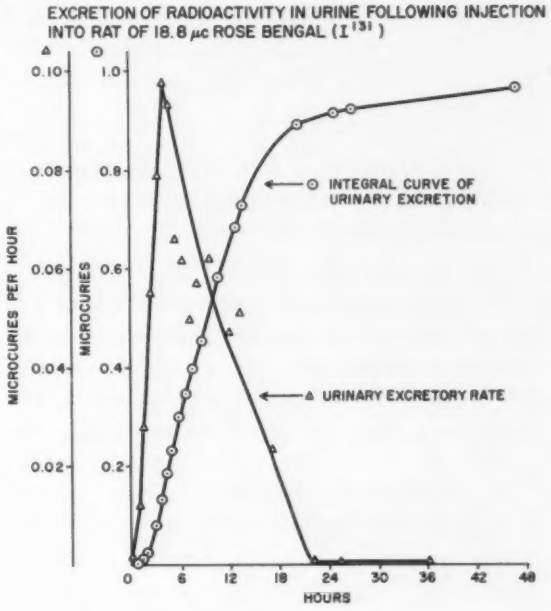

Fig. 4.

Results. The integral of the amounts of I^{131} collected in the urine in each time interval and the corresponding rate of excretion (Fig. 4) show that the most extensive elimination of I^{131} in the urine occurs during the first twenty-four hours.

Forty-six and one-half hours after injection of 18.8 μc of rose bengal, 0.967 μc or 5.1 per cent of the administered dose was excreted in the urine (Table 1). The combined amounts of I^{131} in the urine and thyroid (1.46 μc) totaled 7.8 per cent of the administered dose. This is a minimum

Table I

Radioactivity of rat tissues and excreta forty-six and one-half hours following injection of 18.8μc rose bengal (I^{131})

Tissue	*Microcuries*
Liver	0.221
Stomach	0.036
Intestine, contents, and adherent fat	0.865
Feces expelled during experiment	12.329
Urine	0.967
Thyroid	0.493
Rest of viscera	0.066
Rest of body	0.505
Total	15.482

percentage of radioactive iodine that had dissociated, for some of the radioactivity in the blood and other tissues must also be free I^{131}.

4. Distribution of Radioactivity in Rat Tissues following Administration of Rose Bengal (I^{131}) Directly into the Stomach

To determine whether rose bengal excreted through the biliary tract into the intestine is reabsorbed intact and/or whether I^{131} dissociates from the dye while in the intestine, the following experiment was done.

Material and Methods. Fifty microcuries of rose bengal (I^{131}) were administered to each of 2 rats directly into the stomach. One rat was sacrificed at forty-five minutes and the other at four hours. Selected tissues were dissected out, weighed, digested in sodium hydroxide, and the amount of radioactivity in the tissues determined with a scintillation well-type counter.

Results. I^{131} was absorbed by the intestines, some in the form of the free iodide as evidenced by a concentration of radioactivity in the thyroid, and some as rose bengal (I^{131}) as shown by the accumulation of radioactivity in the liver.

Forty-five minutes after administration of the radioactive dye into the stomach, the thyroid contained 180×10^{-6} μc per mg., and at four hours 460×10^{-6} μc per mg. The corresponding livers contained 9.0×10^{-6} μc per mg. at forty-five minutes, and 8.0×10^{-6} μc per mg. at four hours. Clotted blood and kidney both contained 3.0×10^{-6} μc per mg. at forty-five minutes, and 0.8×10^{-6} μc per mg. at four hours.

The amount of I^{131} that concentrates in the thyroid following administration of rose bengal (I^{131}) into the digestive system is sufficiently small that it could be accounted for as uptake of radioiodide free in the rose bengal solution at the time of administration. It cannot, therefore, definitely be stated from this experiment that I^{131} is dissociated from the rose bengal molecule in the intestines. The experiment does show that small amounts of rose bengal are absorbed from the intestine and end up in the liver.

Taplin, Meredith, and Kade[8] introduced rose bengal (I^{131}) directly into the duodenum of rabbits and reported no radioactivity detectable over the liver upon sacrifice. Their results and ours could differ for a number of reasons, but the most likely reason would seem to be a difference in detection technique.

SUMMARY

1. The time relationships of uptake and excretion and the distribution of radioiodine tagged rose bengal in the rat were determined by measuring the amounts of radioactivity in a variety of tissues at intervals following intravenous injection of the radioactive dye. Radioactivity accumulated in the liver and was excreted into the intestine. Radioactivity also accumulated in the thyroid. Other tissues contained uniformly low amounts of radioactivity.

2. The amount of I^{131} in the thyroid considerably exceeded that which would be expected from the accumulation of free radioiodide present in the solution at the time of injection. A comparison of thyroid uptake of radioactivity following intravenous injection of rose bengal (I^{131}) to thyroid uptake following intravenous injection of NaI^{131} provided evidence of the release of I^{131} from the rose bengal molecule *in vivo* in the rat. A case is mentioned that demonstrates dissociation in man. In a patient with biliary atresia administered radioactive rose bengal, I^{131} was dissociated from the rose bengal molecule, concentrated in the thyroid and excreted in the urine, indicating that the amount of radiation received by the thyroid gland should be considered when radioiodine tagged rose bengal is used.

3. The amount and rate of excretion of I^{131} in the urine of the rat following intravenous injection of rose bengal (I^{131}) was determined. After forty-six and one-half

hours, *5.1 per cent* of the administered radioactivity had been excreted in the urine, most of this in the first twenty-four hours. In the same rat, the amounts of radioactivity were determined in all organs, tissues, and excreta.

4. Following administration of rose bengal (I^{131}) directly into the stomach of rats, the amounts of radioactivity in liver and thyroid were found to be somewhat higher than the amounts in other tissues. This indicated an absorption from the intestine, to a small extent of intact rose bengal (I^{131}) and of free I^{131}.

Robert L. Brent, M.D.
Department of Pediatrics
Jefferson Medical College
1025 Walnut Street
Philadelphia, Pennsylvania

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LONG TERM SEQUELAE OF MASSIVE DOSES OF I^{131} IN RATS*

By PATRICIA W. DURBIN, PH.D., C. WILLET ASLING, M.D., PH.D., MURIEL E. JOHNSTON, M.A., *and* JOSEPH G. HAMILTON, M.D.†
BERKELEY, CALIFORNIA

INTRODUCTION

THE first reports of the selective accumulation of radioiodine by the thyroid gland were made by Hertz, Roberts and Evans,[33] and Hamilton and Soley.[29] In 1942 it was demonstrated by these workers that radioiodine could effect a degree of thyroid destruction comparable to surgery.[24,28,31] Since that time, radioisotopes of iodine, particularly I^{131}, have found widespread clinical applications in the treatment of hyperthyroidism, in metastatic thyroid carcinoma, and in the alleviation of symptoms of certain types of heart disease.[6,30,32,37,41,50,59]

Numerous studies have been made of the alteration of the structure and function of the thyroid gland at different time intervals following various doses of I^{131} in human beings,[2,7,11] dogs,[18,36] monkeys,[44] sheep,[40] rats,[20,39] mice,[21,23,47] birds,[63] and the Atlantic salmon.[35]

Although most studies have dealt with the thyroid gland and its adjacent structures, and with carcinoma of the thyroid and its metastases, several workers have examined the acute effects of massive doses of I^{131} in other tissues. In the clinical experience of Abbatt *et al.*,[1] 50 per cent of patients receiving therapeutic doses of I^{131} developed early transient symptoms of radiation sickness resembling those seen after a single large dose of medium-hard roentgen rays (fatigue, headache, nausea and occasional vomiting). Similar observations were made by Chapman and Evans.[5] However, in rats given doses of I^{131} comparable to those employed therapeutically, no serious symptoms of radiation sickness have been seen.[42] Early lymphopenias have been noted in human beings[59] and rats.[62] A marked degree of injury has been seen in the spleen and lymphatic tissue of rats sacrificed within three weeks after administration of 30 to 70 μc/g. of body weight of I^{131}.[62] Transient cloudy swelling in the kidneys of rats at dose levels of 3.5 μc/g. was observed by Goldberg *et al.*,[20] and alterations in stain intensity of the renal tubular epithelium were reported for rats given 30 μc/g. of I^{131}.[62]

Attempts have been made to estimate the radiation dosage to the thyroid gland,[43] blood,[52] and bone marrow,[45] and to correlate observed damage with I^{131} concentration in tissues other than the thyroid gland. Tracer data have been reported for 6 patients in whom I^{131} was found in moderate concentrations in decreasing amounts in the following order: lung, kidney, pituitary, liver, gonads, spleen, adrenal, and pancreas.[34] At autopsy Godwin *et al.*[13] found measurable amounts of I^{131} in the prostate gland, submaxillary gland ducts, and the spleen of a patient eight hours after the administration of a tracer amount of I^{131}. The distribution of I^{131} has been studied in virgin mice,[46] in lactating mice and their litters,[46] and in young adult female rats.[25] In a comparison of the distribution of tracer and toxic doses (0.33 μc/g. and 30 μc/g.) of I^{131} in rats, tissue concentrations at the tracer level were usually greater than those at the toxic level.[62] The spleen was an exception; at one and two weeks after injection its concentration was greater for the high-level-dose group. It should be emphasized, however, that there was a hundredfold increase in the amount of I^{131} administered to the high-level animals, and that,

* Division of Medical Physics, the Crocker Radiation Laboratory, and the Departments of Medicine, Anatomy, and Radiology of the University of California, Berkeley and San Francisco, California.
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† Deceased.

on an absolute basis, more I^{131} was present in their tissues despite the lesser concentrations.*

Long-term effects of large amounts of I^{131} on tissues other than the thyroid gland are difficult to assess, and published work on this aspect of I^{131} administration is meager. The effects can be divided into three categories: (a) damage in the vicinity of the thyroid gland; (b) alterations in tissues ascribable to thyroid deficiency; and (c) radiation damage in tissues remote from the thyroid gland.

(a) *Tissues Adjacent to the Thyroid Gland.* Radiation damage of the blood vessels in the thyroid region (and of the parathyroid gland when it is deeply embedded in the thyroid) has been noted in patients.[11] Variations from moderate damage to complete destruction of the parathyroid gland, of the recurrent laryngeal nerve, and of the blood vessels in the thyroid region of the rat due to I^{131} have been reported by Goldberg *et al.*[20] In mice, Silberberg *et al.*[56] found that 35 μc/g. of I^{131} damaged the trachea and larynx so severely that death due to obliterative tracheitis often occurred within a few months after the injection. Similar tracheal injury has also been observed in rats.[27] A small but significant number of obstructive tumors of the tracheal tunica propria have been found in mice following administration of 4 to 12 μc/g. of I^{131}.[22] Thyroid neoplasms following I^{131} have been reported by Goldberg and Chaikoff.[16,19]

(b) *Alterations in Tissues Ascribable to Thyroid Deficiency.* Myxedema following thyroid-ablative doses of I^{131} has been reported in monkeys,[44] dogs,[18] sheep,[40] and rats.[60] Effects that are directly attributable to thyroid deficiency include retardation of skeletal growth and maturation (observed in several species),[14,38,55] failure of sexual development in young female mice,[55] arrest of ovarian function (but not of testicular function) in adult mice,[48] and failure of ewes to give birth to viable young.[40] Amenorrhea, and ovarian or testicular atrophy, not explainable on the basis of the ages of the patients, have been reported.[13,59] Alterations in pituitary cytology have been observed by many workers, Goldberg and Chaikoff[15] being among the earliest. Enlargements, or tumors of the anterior portion of the pituitary gland of the mouse ascribable to a combination of thyroid deficiency and radiation received by the pituitary, have been studied by several groups.[17,22,23,47,50] This phenomenon has also been seen in the male Long-Evans rat.[54]

(c) *Radiation Damage in Tissues Remote from the Thyroid Region.* On the chronic level—that is, many months after the administration of I^{131}—clinical findings occasionally included permanent lymphopenia or leukopenia.[52] Trunnell *et al.*[59] reported a case of pancytopenia which was of a severity sufficient to be the cause of death. Two cases of fatal myeloid leukemia following massive and prolonged therapy with I^{131} have recently been described by Seidlin *et al.*[51] Autopsy material from 7 patients who had received doses of I^{131} from 250 to 600 mc given over one- to two-year periods for treatment of metastasizing thyroid carcinoma was examined by Trunnell *et al.*[59] The spleen and lymph nodes from 4 of the patients were notably depleted of lymphocytes, and there was simultaneous abnormal prominence of the reticular network. These tissues had few germinal centers, and the spleen had lost its normal architecture. Permanent leukopenias have also been observed during the chronic administration of I^{131} to sheep.[49] Bone-marrow hypoplasia has been mentioned by Beierwaltes[4] and by Trunnell *et al.*[59] as a temporary contraindication for the use of I^{131} therapeutically. Apart from the fatal pancytopenia noted above, there have been only 2 cases (reported by Godwin *et al.*[13]) of disturbances of the erythropoietic function of the bone marrow: a hyperplasia, and a mild hypoplasia.

The 50 per cent lethal dose at sixty days (MLD_{60}) for I^{131} in rats was established at

* With corrections made for decay, the kidneys of the tracer animals contained 0.0025 μc/g. of I^{131} at one week, and those of the high-level rats contained 0.071 μc/g., or nearly 30 times as much.

85 μc/g. of body weight, by extrapolation from a series of dosages that did not bracket this figure.[26] Direct experimental confirmation of this figure was desired. In addition, it was hoped that a study of the disorders induced in rats at toxic levels would clarify the cause of death. These experiments have therefore been conducted with a broad range of toxic dosages (10 μc/g. to 90 μc/g. at 20 μc intervals). All rats were sacrificed when the survivors of the last group injected had reached fourteen months of age. The patterns of survival, general health and appearance, and microscopic appearance of the tissues of all survivors are described in this paper.

METHODS

The animals used in this study were female rats of the Sprague-Dawley strain, acquired from the original colony when thirty-five to forty-five days of age. After rejection of the lightest and heaviest 10 per cent of each shipment, the animals were housed on wood shavings in stock cages and were fed tap water, and either "Diet 14" developed by the U. C. Institute of Experimental Biology or Purina Laboratory Chow *ad lib.* At the age of fifty-two to sixty days they were weighed, earmarked, randomized into groups of 8 to 10 animals, and injected with I^{131}.

The I^{131} was obtained from Oak Ridge National Laboratory in 300 mc lots; it was assayed and diluted to the appropriate concentration with isotonic saline containing 5 mg./ml. of sodium sulfite. The desired dosage, 10 μc/g.* to 90 μc/g. (1.5 to 13.5 mc I^{131} per rat), was obtained by varying the administered volume according to the weight of the animal. Injections were made into the surgically exposed external jugular vein under light ether anesthesia; the incision was closed with wound clips. After injection the animals were housed in stock cages in groups of 3. The cages were separated from one another by lead sheets 5/8 inch thick in an attempt to minimize cross-irradiation of gamma rays from one rat to another.

Whenever possible, moribund animals were autopsied, and the tissues fixed for histologic examination. All animals were weighed once each week for the first eight weeks and monthly thereafter; at each weighing they were examined for gross appearance. One year after the injection of the last group, all animals received a 10 μc tracer dose of I^{131} intramuscularly and were sacrificed twenty-four hours later. A complete autopsy was performed on each animal. The thyroid region of the trachea was removed (no visible thyroid gland remained), and the gamma-ray activity was measured.[25]

The following tissues were taken for histologic examination: thyroid remnants (dissected microscopically from the trachea after fixation), liver, lung, spleen, kidney, adrenal, mesenteric lymph nodes, thymus, ovary, uterus, and pituitary. Tumors, uterine growths, and unusually large lymph nodes were also taken when present. The trachea and ovary were fixed in Bouin's fluid, the pituitary in Zenker-formol, and all other tissues in 10 per cent neutral formalin. The spleen, pituitary, and left adrenal were weighed on a torsion balance. Tissues were prepared for histologic examination by the paraffin method using dioxane for dehydration. Sections were cut at 6 μ, and stained with Harris's hematoxylin and eosin (the pituitary was the only exception; it was cut at 4 μ, and stained with Mallory-azan).

RESULTS AND DISCUSSION

Survival of rats was markedly impaired at doses of 30 μc/g. and above (Table 1). The mortality rate was progressively higher with dose, so that rats receiving 90 μc/g. had only one-seventh the average life expectancy of those receiving 30 μc/g. In fact, the morbidity in the 90-μc/g. group was so high that it was necessary to sacri-

* The lowest dose employed, 10 μc/g., is approximately 3 times the thyroid-destructive dose established by Goldberg *et al.*[20] for rats on a low-iodine diet.

TABLE I

SURVIVAL OF FEMALE SPRAGUE-DAWLEY RATS FOLLOWING INTRAVENOUS ADMINISTRATION OF A SINGLE MASSIVE DOSE OF I^{131} AT FIFTY-FIVE DAYS OF AGE

Days after Injection	Per Cent Survival					
	Controls 10 Rats	10 μc/g. 10 Rats	30 μc/g. 28 Rats	50 μc/g. 17 Rats	70 μc/g. 20 Rats	90 μc/g. 19 Rats
5	100	100	82	65	70	90
15	100	90	82	65	65	90
30	100	90	79	65	65	63
60	100	90	79	59	55	*47**
90	100	90	79	59	*50*	47
120	100	80	75	59	45	42
150	100	80	72	59	45	42
180	90	80	68	*53*	45	37
240	90	80	64	53	45	26
300	90	80	61	47	35	21
360	90	80	57	41	30	21
420	90	80	*50*	35	30	†

* 50% survival time italicized.
† 90 μc/g. group sacrificed at one year postinjection, all others at 450 days or longer.

fice the survivors early to assure adequate anatomic and histologic studies.

The 50 per cent survival time in days plotted semilogarithmically as a function of I^{131} dose is shown (Fig. 1). A straight-line relationship was obtained with a slope of 0.022 $(\mu c/g.)^{-1}$. Extrapolation to zero dose yields a mean survival time of eight hundred and forty days, which is in agreement with the mean life span of seven hundred and sixty days determined for normal rats of this species in another laboratory.[8] The equation for the shortening of life span by I^{131} thus becomes $MLS = 840e^{-.022d}$, where *MLS* is mean life span and *d* is the I^{131} dose in μc/g. It should be emphasized that the slope may be different for rats younger or older than fifty-five to sixty days at the time of I^{131} administration.

Figure 2 shows that a marked reduction in growth, as judged by body weight, occurred in all groups receiving I^{131}. The graph presents data derived only from surviving animals. There was no statistically significant difference between the weights of the animals in the 10- to 70-μc/g. groups, therefore a single curve has been drawn.

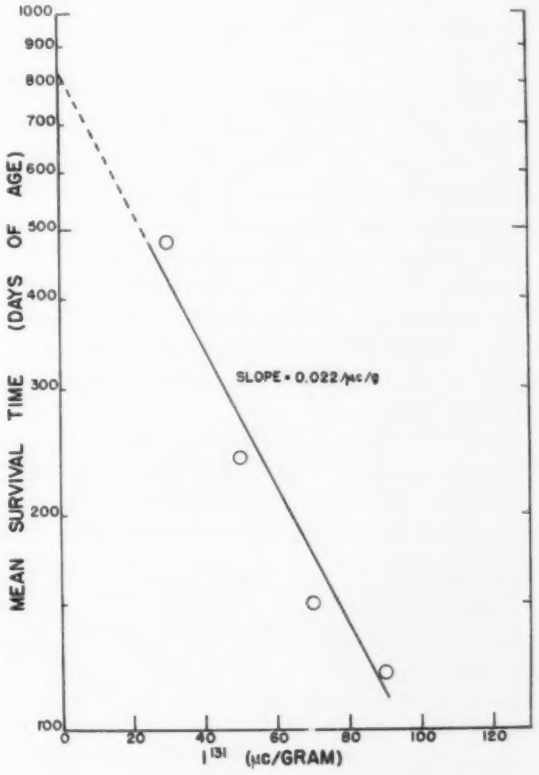


FIG. 1. Graph showing survival time of rats as a function of the dose of I^{131}.

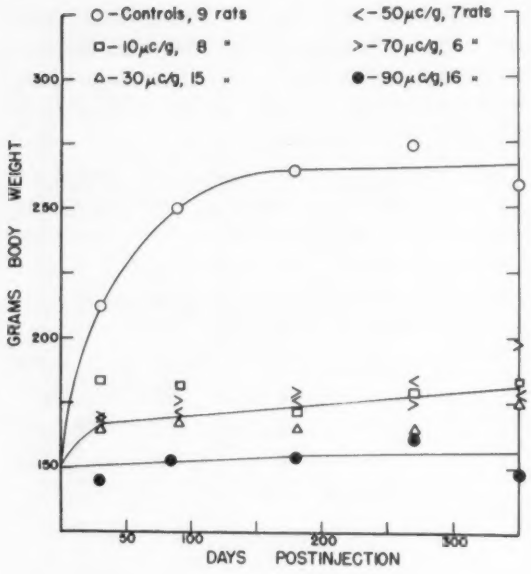


FIG. 2. Retardation of growth of rats as a function of the dose of I^{131}.

The weights of the 90-μc/g. group were significantly lower, and a separate curve has been shown.

The gross appearance of the rats deteriorated progressively with increasing dose level, notably in terms of skin condition and general untidiness. Malocclusion of the incisors also became more evident.

At autopsy all the 10-μc/g. group appeared normal so far as the amount of subcutaneous and internal fat and the amount of lymphatic tissue (mesenteric and cervical lymph nodes, Peyer's patches, and thymus) were concerned. However, in at least one-half of the rats in the 30- through 90-μc/g. groups, fat was scanty or absent, and the total amount of lymphatic tissue was greatly reduced. Generally, the ovaries presented a degenerate appearance; they were reduced in size, pale, and often cystic or fibrotic. Along with this, the uteri were small, thin-walled, and often poorly vascularized, and at times contained fibroids.

The spleen and the adrenals of all treated animals were, even to the naked eye, reduced in size (Table II). It can be seen from their weights that this reduction was of the order of 50 per cent at all dose levels. The pituitary weights of the treated rats were significantly lower than those of the controls. Although the differences between the weights of the spleen, adrenal, and pituitary gland in the iodine-treated and the control animals were significant ($P<.01$),

TABLE III

PERCENTAGE BODY WEIGHT OF SPLEEN, LEFT ADRENAL AND PITUITARY OF NORMAL RATS AND THE MEAN OF ALL SURVIVING I^{131} TREATED RATS

Organ	Percentage Body Weight (mg./100 g.)		
	Controls 12–20 Rats*	I^{131} Treated 43 Rats	"P"
Spleen	194 ±7	128 ±4	<.01
Adrenal	12.5 ± .4	10.7 ± .4	<.01
Pituitary	5.0 ± .2	6.7 ± .3	<.01

* 20 control spleens and adrenals, 12 control pituitaries.

TABLE II

BODY WEIGHT AND WEIGHT OF SPLEEN, LEFT ADRENAL AND PITUITARY OF RATS SURVIVING AT LEAST ONE YEAR AFTER A SINGLE MASSIVE DOSE OF I^{131}

Dosage I^{131} μc/g.	No. of Survivors	Age Range, Days	Body Weight, Grams	Organ Weights in Milligrams		
				Spleen	Adrenal	Pituitary
Control	21	300–425	275 ± 6	506 ± 20	34.2 ± 1.0	14.5 ± .5*
10	8	565	177 ± 4	217 ± 14	17.5 ± 1.1	12.2 ± .6
30	14	475–565	186.5 ± 7	230 ± 14	19.0 ± 1.4	11.5 ± .5
50	4	535–565	181 ± 4	255 ± 23	19.7 ± 1.4	12.6 ± .5
70	5	505–565	182 ± 14	218 ± 25	16.1 ± 1.2	12.1 ± 1.2
90	12	405–475	155 ± 7	207 ± 15	18.9 ± .9	10.6 ± .4

* Pituitary weights available for only 12 control rats.

the differences between these weights in the various dose-level groups were not significant. The data for these tissues were therefore used without differentiation of dose level in calculating their proportionality to body weight (Table III). The spleen and adrenal gland weights were reduced out of proportion to body weight; the pituitary, on the other hand, was slightly larger in proportion to body weight.

Functional measurements of the adequacy of thyroid destruction are shown in Table IV. The uptake by paratracheal tissue of a tracer dose of I^{131} given eighteen to twenty-four hours before autopsy was reduced to less than 1 per cent of the normal. The red blood cell-to-plasma I^{131} ratio was somewhat increased, indicating a reduction in the protein binding of this tracer dose.[49]

Details of histologic findings[3] have been published. The summaries are presented here.

ENDOCRINE GLANDS

Thyroid Gland. In accord with the findings from the functional tests, no residual thyroid tissue was found in any of the rats (Fig. 3–6). At the lowest level, 10 μc/g., there was complete thyroid destruction. There was an adequate inflammatory reaction to the degenerating tissues, with consequent fibrous replacement of the glandular elements. This fibrous reaction was still effective at the 30-μc/g. level, but had begun to be impaired. Necrotic material persisted, and giant multinucleated cells were found occasionally, possibly as a foreign-body reaction. Further transitional stages were seen at the 50- and 70-μc/g. levels. Substantial masses of necrotic substance persisted, but with some evidence of fibrous invasion at the periphery. At the highest level, 90 μc/g., there was almost complete failure of the replacement mechanism. The necrotic tissue not only persisted in large masses but also showed no tendency to become homogeneous; rather, it retained a regional architecture simulating the arrangement of the burned-out thyroid. It is suggested that the radiation escaping from the thyroid gland in early phases destroyed the neighboring connective tissue elements, and thus inhibited repair.

TABLE IV

THYROIDAL I^{131} ACCUMULATION AND RED BLOOD CELL TO PLASMA I^{131} RATIO ONE YEAR AFTER ADMINISTRATION OF A SINGLE MASSIVE DOSE OF I^{131}

Dose of I^{131} μc/g.	Per Cent I^{131} Thyroid and Trachea	I^{131} RBC: Plasma
Control	9.3 ± .7 (21)*	.63 ± .04 (6)
10	.06 ± .003 (16)	.73 ± .02 (16)
30	.04 ± .005 (14)	.73 ± .02 (12)
50	.03 ± .007 (4)	.73 ± .02† (9)
70	.04 ± .005 (5)	
90	.05 ± .01 (12)	.76 ± .02 (11)

* (n) indicates number of specimens.
† 50 μc/g. and 70 μc/g. groups combined.

Pituitary Gland. This gland showed the characteristic changes that follow thyroidectomy (Fig. 7–9). At the 10- and 30-μc/g. levels the acidophils were reduced in number and degranulated. "Thyroidectomy basophils" were very common, and additional basophils were found which probably represented new crops of cells. The total number of basophils was usually increased. Vascularity was variable, but occasionally some sinusoidal dilatation was seen. These alterations corresponded to the changes following thyroidectomy with I^{131} reported by Goldberg and Chaikoff,[15] and following surgical thyroidectomy (Severinghaus *et al.*[53] and Zwecker *et al.*,[64] among others). From the 50-μc/g. level up, specifically stained cells were rare or nonexistent; the gland consisted almost entirely of chromophobes. Vascularity was progressively increased until the dilatation of the sinusoids appeared to be crowding out the cells. The changes at the higher dosages may not be attributed to thyroid deficiency alone, which was already presumably maximal at the lowest dose. Effects of irradiation of the pituitary by internal sources have been little studied, although the chromophobe tumors of the anterior pituitary glands of mice following administration of radioio-

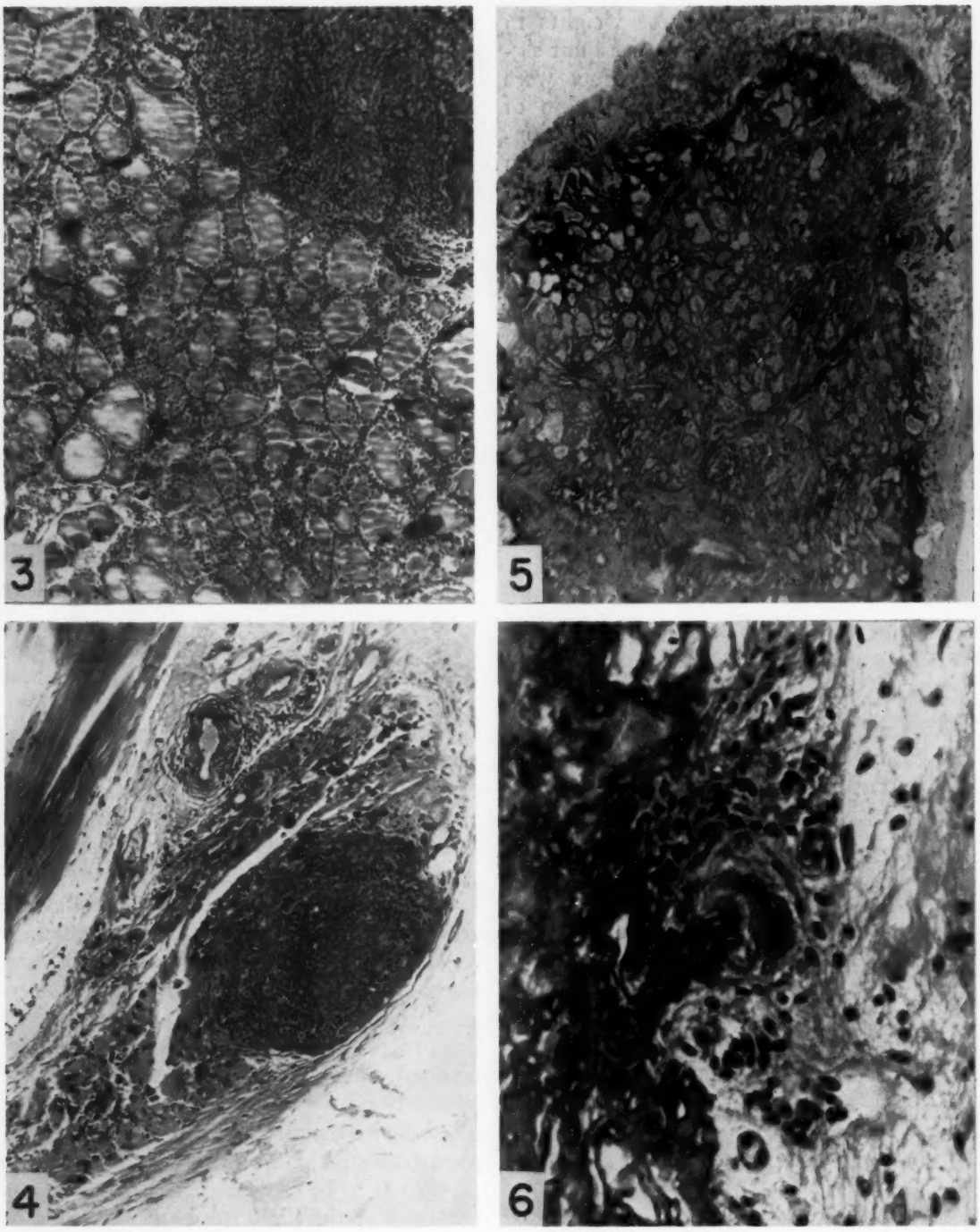


FIG. 3–6.

3. Normal thyroid gland, with parathyroid. (H. and E., ×90.)
4. Paratracheal tissue after I^{131}, 10 μc/g. body weight. Thyroid is completely replaced by fibrous tissue and macrophages; a fragment of parathyroid remains. (H. and E., ×90.)
5. Paratracheal tissue after I^{131}, 90 μc/g. body weight. An unresorbed necrotic coagulum occupies the thyroid region and is encapsulated with fibrous tissue containing giant cells (as at x). No parathyroid remained. (H. and E., ×90.)
6. Higher magnification of region at x in Figure 5. Note multinucleated giant cell. (H. and E., ×420.)

dine have been shown to be a consequence of both thyroid deficiency and direct irradiation of the pituitary.[17,22,47] Recently, Tobias *et al.*[58] have irradiated the pituitary glands of dogs and rats with high-energy deuterons. Although rather high dosages (12,600 rep or more) are required to produce complete pituitary degeneration in rats in a short time, lower dosages (6,300 rep) produce a gland consisting only of chromophobes after a nine month postirradiation interval. It remains to be seen whether still lower doses within the range of the whole-body dose in this experiment (estimated to be of the order of 800 rep at the 90-μc/g. level) would result in a similar degeneration, if a still longer time were allowed to elapse.

Adrenal Gland. The adrenal cortex was thinned at all dosage levels (Fig. 10–12). The fasciculata was reduced in width and vascularity. The cords became indistinguishable as such or were arranged as sheets of cells. The reticularis was also reduced in width and often showed dilated sinusoids. The cells of both these zones were often small and atrophic, with pyknotic nuclei. The glomerulosa was virtually normal at doses up to and including 70 μc/g. At the 90-μc/g. level it was atrophic and difficult to recognize.

At all except the highest dosage, the adrenal gland changes corresponded to those expected after thyroid deficiency; the structural alterations were attributable both to lack of thyroid hormone and to reduction of pituitary secretion of adrenocorticotropic hormone. Evans *et al.*,[10] and Deane and Greep[9] demonstrated that the glomerulosa showed little damage following surgical thyroidectomy, but that the fasciculata and reticularis are moderately atrophic. The explanation for the glomerulosa damage at the highest dose level is not clear, but apparently does not rest entirely on an endocrine basis. It has been shown that even after total hypophysectomy the glomerulosa remains intact.[57]

Ovary. Ovarian degeneration was seen in virtually all animals treated with radioiodine. At the lower levels, persisting degenerate corpora lutea and a few small follicles were seen. At the 50-μc/g. level and above, however, the ovaries were very small and —with a single exception—showed no evidence of cycling. The ovarian atrophy is consistent with the impaired pituitary function that follows thyroid destruction. The ovaries in these animals corresponded in all important aspects to those described by Evans *et al.*,[10] following surgical thyroidectomy under time conditions almost identical with the ages and intervals in this experiment. None of the changes was felt by us to represent the primary action of the radioiodine in the ovary.

LYMPHOPOIETIC TISSUES

Thymus. The thymus, despite the variability within groups, tended to be smaller with increasing dose. There was increasing brown-fat replacement of the lymphatic tissue from the 10- to the 70-μc/g. dose level, but even at the highest level, some depleted lymphatic tissue was found with the replacement adipose tissue. Epithelial cords or sheets suggesting thyroidal epithelium, or follicles resembling those of the thyroid, were seen in a number of control animals. From the 10- through the 70-μc/g. groups there was an increasing occurrence with dose of such epithelial remains. In the 90-μc./g. group this type of tissue was not found. Such epithelium may represent "thyroid rests," its presence initially being related to the close embryologic derivation of thyroid and thymus glands. Further experiments are required for analysis of its significance.

Lymph Nodes. The mesenteric lymph nodes† showed appreciable damage at all dose levels. The cortical structure was thinned or interrupted and lymphopoiesis was reduced in varying degrees (Fig. 13–15). There was some gradient in this effect, so that at the higher dose levels it was increasingly difficult to find follicles exhibiting any indication of lymphocyte formation. Throughout the series the medulla was depleted of lymphocytes, and at the higher

† Cervical lymph nodes sampled showed alterations similar to those of the mesenteric lymph nodes.

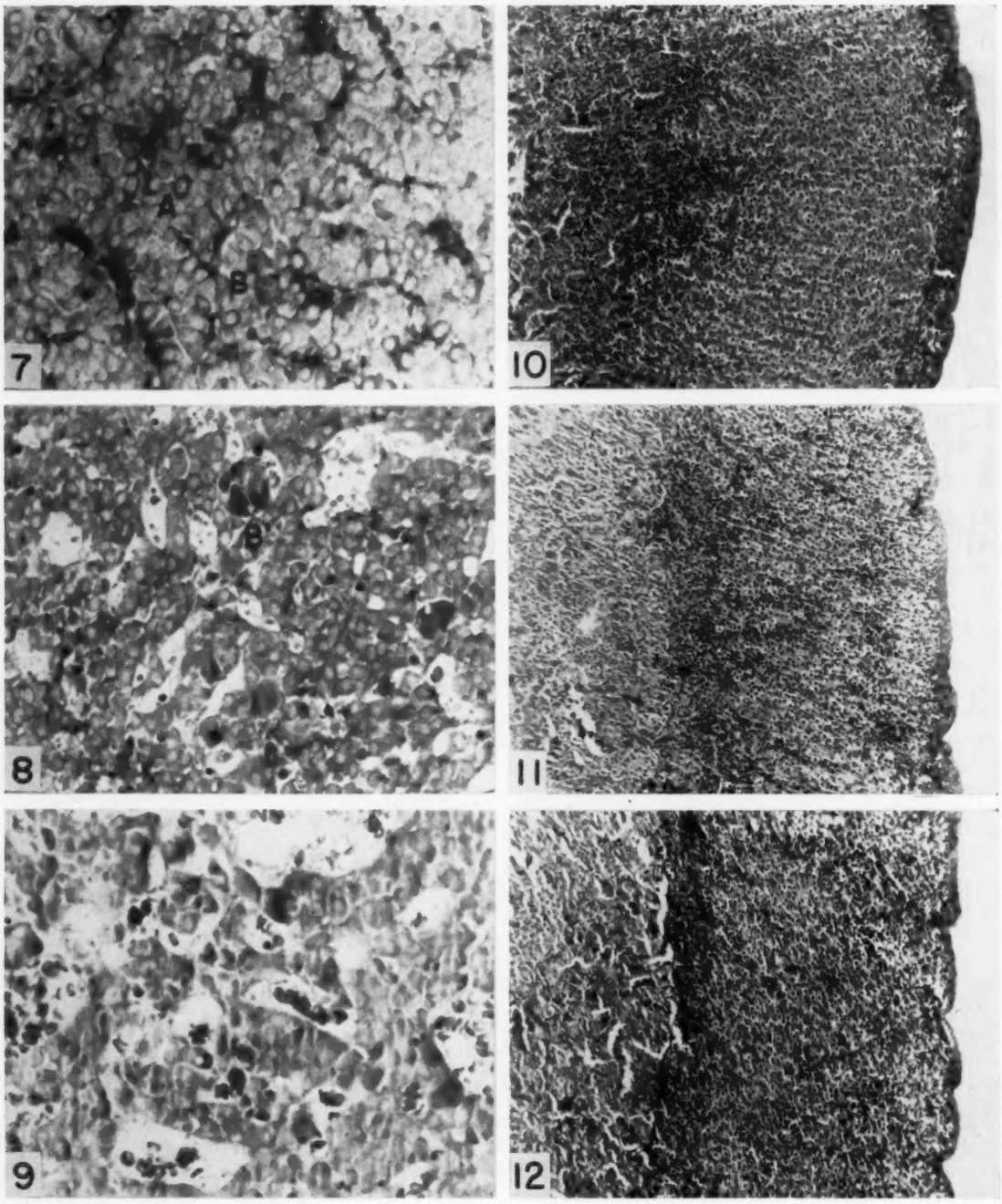


FIG. 7–12.

7. Normal anterior pituitary gland, showing acidophils (as at A), basophils (as at B), and chromophobes (remaining glandular cells). (Mallory-azan, ×155.)
8. Anterior pituitary gland after I^{131}, 10 μc/g. body weight. Typical "thyroidectomy" changes are degranulation of acidophils and presence of "thyroidectomy" basophils (as at B′). (Mallory-azan, ×155.)
9. Anterior pituitary gland after I^{131}, 90 μc/g. body weight. Chromophobes predominate; dilated sinusoids were commonly found. (Mallory-azan, ×155.)
10. Normal adrenal cortex. (H. and E., ×30.)
11. Adrenal cortex after I^{131}, 10 μc/g. body weight. The cortex is narrowed, especially in the zona fasciculata and reticularis. (H. and E., ×30.)
12. Adrenal cortex after I^{131}, 90 μc/g. body weight. Zonal architecture is completely lost. (H. and E., ×30.)

dose levels specimens could be found that had no lymphocytes.

Spleen. The spleen generally showed some impairment of the white pulp at the lower dosage levels. The resultant reduction of lymphatic tissue rendered the framework conspicuous. It was difficult to establish any gradient of damage through the lower-dosage groups because of the individual variation within the groups. The lymphatic damage became much more substantial at the 70-μc/g. level, and at the 90-μc/g. level it was very high. The red pulp remained reasonably normal throughout the lower dosages, and showed only mild damage in most of the 70-μc/g. animals and in at least half the 90-μc/g. group.

Thus it is seen that in all the lymphatic tissues there was some gradient of increasing damage with increasing dose. It seemed likely that the radiosensitivity of these tissues accounted for their alterations. Profound lymphopenia has been observed during the first three weeks following a 30-μc/g. dose of I^{131} in the same strain of rats.[62] It was noteworthy that these tissues were seldom able to accomplish appreciable regeneration even in the long postirradiation interval under study. Lymphatic tissues, particularly the thymus, are under endocrine control to a degree, and become depleted as a result of pituitary hypofunction. It is possible that the impaired regeneration may in part be attributed to this.

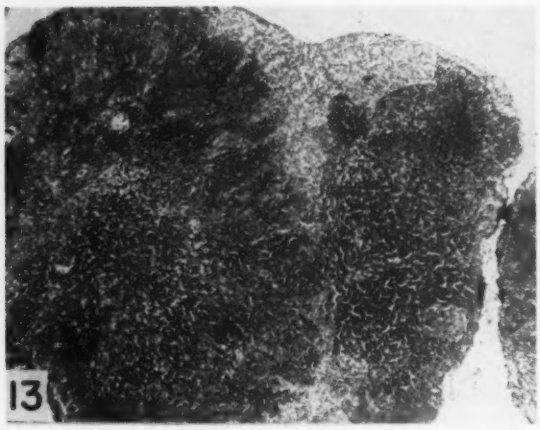
OTHER VISCERA

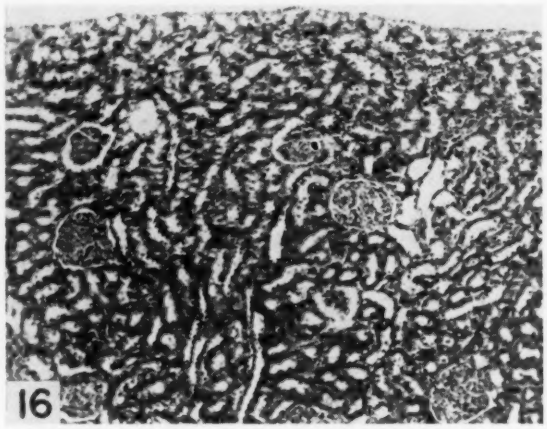
Kidney. There was a clearly discernible gradient of renal damage with increasing dose which was most marked in the glomeruli. The blood vascular components of the glomeruli were reduced, and they showed increased fibrosis and reduction in size; in the extreme, they were scarred and degenerate (Fig. 16–18). There was a less conspicuous gradient in tubular damage, visible chiefly at the higher dose levels as a vacuolar degeneration or atrophy. The best evidence of tubular damage was gained from an increase with dose in the number of glomeruli that could be seen in a low-power field. The inference was drawn that the tissues between these glomeruli had become degenerate or atrophic, reducing the intervening space. A third phenomenon associated with the radioiodine administration was deposition of golden-brown pigment in the tubular epithelium, particularly deep in the cortex and near the junction with the medulla. This was seen most often at the 10- and 30-μc/g. dose levels; thereafter, though the majority of specimens might still show small amounts of pigment, this particular phenomenon became less common. Evidence of damage in the medulla was not clear-cut at any dose level.

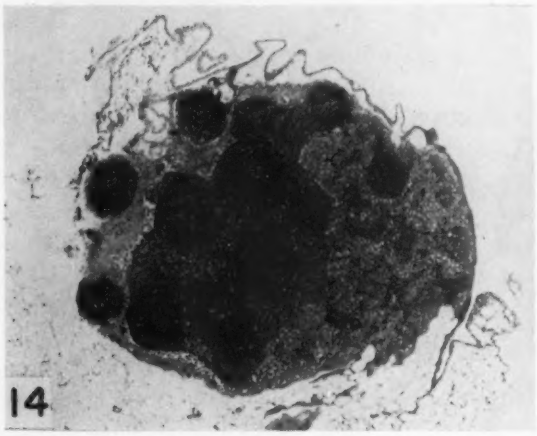
Renal damage may be attributed to irradiation suffered in the metabolism and excretion of large amounts of radioiodine. Cloudy swelling of the kidney has been seen shortly after administration of small doses of I^{131}. It is reasonable to assume that in the excretion of the much larger quantities of I^{131} used in these studies the early damage was even more severe, and—in at least some nephrons—was irreparable. In fact, at the higher dosages (90-μc/g. and possibly 70-μc/g.) the proportion of damaged tissue was high enough to suggest that renal reserve, even in the survivors, was dangerously low.

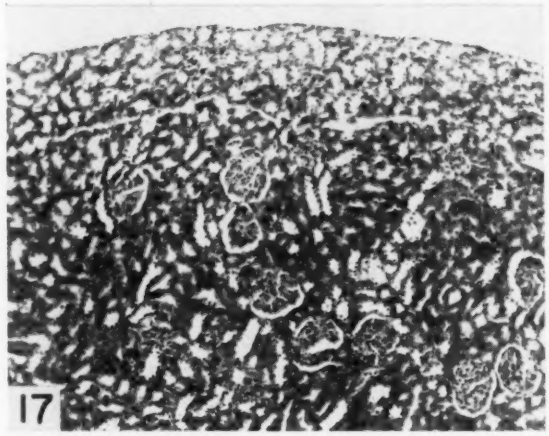
Liver. The liver was resistant to damage at the lower dosage levels. The only noteworthy finding was an appreciable incidence of either scattered or fairly uniformly distributed tiny clusters of dark round cells, the identities of which remain questionable. These may represent ectopic sites of blood formation. At the 90-μc/g. dose level many of the specimens showed appreciable damage, but only rarely had this reached the point where one could assume impairment of hepatic function.

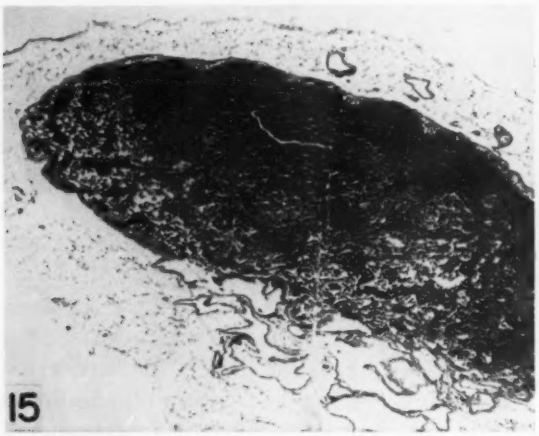
Lungs. There appeared to be nothing diagnostic of radioiodine toxicity in the lungs of even the high-level animals; virtually all the kinds of pathology (chiefly identifiable as subclinical pneumonitis) that were found in the treated animals could also be found in the controls. However, it is possible that these findings were encountered in higher incidence or were











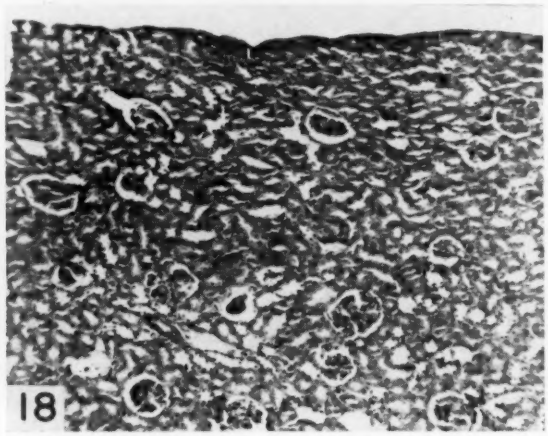


FIG. 13–18.

13. Normal mesenteric lymph node. (H. and E., ×20.)
14. Mesenteric lymph node after I^{131}, 10 μc/g. body weight. (H. and E., ×20.)
15. Mesenteric lymph node after I^{131}, 90 μc/g. body weight. (H. and E., ×20.)
16. Normal kidney cortex. (H. and E., ×45.)
17. Kidney cortex after I^{131}, 10 μc/g. body weight. Slight damage. (H. and E., ×45.)
18. Kidney cortex after I^{131}, 90 μc/g. body weight. Marked glomerular and tubular damage. (H. and E., ×45.)

more extensive in a given section in the treated groups.

NEOPLASMS

Observable neoplasms at some point along the mammary line developed in 9 (12 per cent) of the 72 rats that survived longer than two months after the administration of the radioiodine.* Three of these animals with large tumors were sacrificed at six to eight months of age. Attempts to transplant these tumors were not successful. The number of tumors among the sixty-day survivors in each dosage group, the type of tumor, and the age when the tumor was first noted are shown in Table v. The incidence of mammary tumors did not seem to be a function of dose, although there was a suggestion that these tumors appeared sooner at the two highest dose levels.

It should be emphasized that no tumors of either the pituitary or thyroid gland were seen. Benign uterine fibroids were observed occasionally; however, neither their incidence nor the dosage levels at which they occcurred appeared to be significant.

The finding of mammary tumors in the animals in this experiment is of questionable importance. Davis *et al.*[8] have recently reported the tumor incidence in a large colony of normal Sprague-Dawley rats (the strain used in this experiment). Fifty-four per cent of the females developed mammary tumors; 13 per cent of these tumors developed before the animals were five hundred and forty days of age; and 12 per cent of all tumors were classified as malignant. On the basis of these figures, it would be expected that in our experiments, at least 7 of the sixty-day survivors would develop mammary tumors before the age of five hundred and forty days (9 were observed), and that one of these might possibly be malignant. Neither the number of tumors we observed nor the time of their appearance was significantly different from normal expectancy. On the other hand, the number of malignancies is of real significance (8 of the 9 tumors were classified as malignant by use of the criteria set forth by others).[8] We are not aware of any studies

* Animals that died in the first two months postinjection were excluded on the presumption that acute radiation syndrome was the most likely cause of death. The maximum age attained by these excluded animals was four months; none of the animals in this experiment had developed tumors at this age.

TABLE V

INCIDENCE AND CLASSIFICATION OF MAMMARY TUMORS OBSERVED IN SPRAGUE-DAWLEY FEMALE RATS SURVIVING MORE THAN SIXTY DAYS AFTER A SINGLE MASSIVE DOSE OF I^{131}

I^{131} Dose $\mu c/g.$	Number of Survivors	Number of Mammary Tumors	Tumor Type and Age When First Observed
Controls	21	none	
10	9	none	
30	22	3	1. Duct adenoma showing early malignant changes (571 days) 2. Medullary carcinoma (474 days) 3. Squamous cell carcinoma with a metastasis to a lymph node (474 days)
50	10	none	
70	11	3	1. Fibroadenocarcinoma, cystic (226 days) 2. Adenocarcinoma of the mammary ducts (571 days) 3. Benign duct adenoma (571 days)
90	30	3	1. Spindle cell sarcoma or adenosarcoma (220 days) 2. Adenocarcinoma, papillary and cystic (183 days) 3. Fibrosarcoma with a metastasis to the surface of the stomach (443 days)

relating thyroid deficiency to an increased incidence of mammary tumors in rats. Rat mammary tissue (both lactating and nonlactating) has been demonstrated to accumulate and secrete radioiodine.[12,46] In light of these observations, the possibility should not be overlooked that the occurrence of a relatively high proportion of malignancies among the mammary tumors was a direct consequence of radioiodine administration.

REMARKS

The structural alterations in these rats appeared to fall roughly into three groups: those attributable to endocrine disturbances; those attributable to irradiation; and those which appeared to reflect both endocrine disturbance and irradiation damage.

The cause of late deaths among animals receiving these high dosages of radioiodine requires analysis. Although the most complete studies have been made on tissues from the survivors rather than on animals that succumbed, it must be remembered that some of these survivors would have been expected to die shortly, and that this expectation was so high for the 90-μc/g. group that they were sacrificed relatively early. No single cause of death may be advanced from this study. However, in the presence of a marked metabolic deficit (hypothyroidism and pituitary deficiency), reduced lymphopoietic activity (atrophy of lymphatic tissues), reduced capacity to respond to the stress of inflammation (adrenal cortical atrophy), and inadequate renal reserve (chronic nephritis), it is reasonable to believe that many animals would not survive even a moderate infection, if such were present. There was appreciable incidence of subclinical pneumonia, both in controls and in the injected rats. It is most likely that some intercurrent infection was the immediate cause of death in animals whose condition was much below normal owing to endocrine and radiation pathology.

Finally, it should be pointed out that the experiments reported here have provided a firm basis for explaining a number of pathologic observations made on human subjects following massive I^{131} therapy.[13,52,59]

SUMMARY

1. Female rats fifty-five to sixty days of age were injected with I^{131} at dosages ranging from 10 to 90 μc/g. body weight, and during the ensuing year observations were made on impairment of health, on mortality, and on gross and microscopic pathology.

2. Growth was retarded at all dose levels, and most severely at the highest level. The animals appeared progressively less healthy with increasing dose.

3. Life expectancy was appreciably reduced at levels of 30 μc/g. and above. An exponential relationship was obtained between mean life span and I^{131} dose which can be described by the equation: mean life span $= 840e^{-.022\ \mu c/g.I^{131}}$.

4. Thyroid destruction was complete at all dosage levels. Cellular repair mechanisms (fibrosis and phagocytosis) were impaired in this region at the higher dosages.

5. Anatomic findings that were attributable to radiation included thyroid destruction, atrophy of lymphopoietic tissues (spleen, lymph nodes and thymus), chronic renal damage, and possibly liver damage.

6. Findings attributed to endocrine deficiency were hypothyroidism (including growth retardation), anterior pituitary "thyroidectomy" changes, and ovarian and adrenal cortical atrophy. At the highest dosage levels there were suggestions of additional radiation damage to pituitary and adrenal glands.

7. Mammary tumors appeared in a number of rats at a substantially earlier age than is characteristic for the strain; no correlation of tumor incidence with I^{131} dosage was observed.

8. Late deaths are believed to have been caused by intercurrent infection (chiefly pneumonia) in the presence of reduced

renal reserve, adrenal cortical hypofunction, reduced lymphopoietic activity, and severe hypothyroidism.

Crocker Laboratory
University of California
Berkeley 4, California

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METABOLISM OF RADIO-RUTHENIUM IN THE RAT*

CONSIDERATION OF PERMISSIBLE EXPOSURE LIMITS

By ROY C. THOMPSON, MAURICE H. WEEKS,† O. LEROY HOLLIS,‡ JOHN E. BALLOU, *and* WILLA D. OAKLEY§

Biology Operation, Hanford Laboratories, General Electric Company
RICHLAND, WASHINGTON

LIKE many other relatively rare elements, ruthenium has recently become of interest to the biologic scientist because of its prominence in the spectrum of products formed in the nuclear fission of uranium. The ruthenium isotopes of major significance among the fission products are Ru^{103} and Ru^{106}. Ru^{103} is a beta-emitter (maximum energy, 0.2 mev.) with a half-life of forty days. At ninety days following instantaneous fission of U^{235} it is responsible for 7.2 per cent of the total fission product radioactivity.[5] Because of its short half-life, by one year post fission it accounts for less than 1 per cent of the total radioactivity.

Ru^{106} is a beta emitter (maximum energy 0.04 mev.) with a half-life of three hundred and sixty-five days. The daughter of Ru^{106}, rhodium 106, is also a beta-emitter (maximum energy, 3.5 mev.) with a half-life of thirty seconds. The energy release in the $Ru^{106} \rightarrow Rh^{106} \rightarrow Pd^{106}$ (stable) chain is therefore attributable largely to Rh^{106}. However, the biologic distribution of this released energy will be determined by the physiologic behavior of the parent Ru^{106}, because of the extremely short half-life of Rh^{106}. At ninety days following instantaneous fission of U^{235}, Ru^{106} and Rh^{106} are responsible for less than 1 per cent of the total fission product radioactivity, but after one year, they account for 2.4 per cent.[5]

Very little previous work has been done on the biologic behavior of ruthenium. The presently established maximum permissible limits for Ru^{106} in the human body, in air, and in water[7,10] are based on limited studies with a small number of rats.[3,8] Studies on the distribution and retention in rats of inhaled Ru^{106} were reported by Dailey *et al.*[1] More recently, Scott *et al.*[9] reported on the short-term retention in rats of intravenously administered ruthenium.

Our interest in ruthenium was stimulated by the finding of Hanson and Browning[4] that approximately 3 per cent of intragastrically administered Ru^{106} was absorbed by chickens. This absorption value was so much higher than the value of <0.05 per cent reported for the rat[3,8] that an experiment was performed to check the gastrointestinal absorption of ruthenium in the rat. The finding in this experiment of a much higher absorption than was previously reported led to a more complete study of ruthenium metabolism which is detailed in this paper. Coincident with our program on the metabolism of ruthenium, studies have been made at the Argonne National Laboratory on the radiotoxicity of the element.[11]

METHODS

Ruthenium Radioisotope Solutions. The isotope employed in all experiments was Ru^{106} obtained from Oak Ridge as "carrier-free chlorides" in 6 *N* HCl solution. The specific activity was in the range of 4–10 c/gm. ruthenium. In most of the experiments to be described, the HCl solution, as obtained from Oak Ridge, was diluted, the pH adjusted as required with NaOH, and this solution administered to the animals without further chemical treatment. These solutions probably contained both Ru(III) and Ru(IV), hydrolyzed to a varying de-

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† Present address: Army Chemical Center, Maryland.
‡ Present address: Dow Chemical Co., Freeport, Texas.
§ Present address: Convair, Fort Worth, Texas.

gree depending upon the pH. In all experiments, unless otherwise noted, the dilution of the 6 *N* HCl solution and pH adjustment were made twenty-four hours prior to administration of the solution to the rats.

The decision to employ the Oak Ridge solution without attempting to standardize the valence state of the ruthenium was reached after experiments with various chemically treated solutions of ruthenium had shown little effect of the treatment on ruthenium absorption from the gastrointestinal tract. In these experiments the ruthenium was oxidized to the tetravalent state with NaOCl, reduced to the trivalent state with $SnCl_2$, and these solutions fed after various periods of standing.

In studies of the effect of specific activity on absorption of Ru^{106} from the gastrointestinal tract, ruthenium carrier, as the chloride, was added to the 6 *N* HCl Ru^{106} solution and allowed to stand for two months before dilution, pH adjustment, and administration to the rats. It was felt that this long period of standing in acid solution would insure homogeneity of the stable and radioactive ruthenium. Earlier attempts to obtain homogeneous solutions by oxidizing the isotope mixture and distilling the volatile tetroxide were accompanied by such low and variable yields that this method was abandoned in favor of the procedure of prolonged standing in acid solution.

Animal Procedures. Rats employed were of the Sprague-Dawley strain, and except as otherwise noted were maintained on an *ad libitum* diet of Puria Laboratory Chow. Intragastric administration was accomplished via stomach tube without anesthesia. Light ether anesthesia was employed for intravenous injections which were made via the great saphenous vein. Intratracheal injections were made by surgical exposure of the trachea under nembutal anesthesia. In the chronic feeding studies, Ru^{106} was added to the drinking water which was adjusted to pH 2 and was continuously available. Water consumption was measured in all such experiments. All-glass metabolism cages were employed in experiments requiring the collection of urine and feces.

Sampling and Counting Procedures. Animals were sacrificed by decapitation. In most cases, tissues were minced, and air-dried on stainless steel plates for direct beta counting. Feces samples and tissue samples too large to be counted by this procedure were partially digested with nitric acid, care being taken to prevent evaporation to dryness. Under the conditions employed there was no significant loss of Ru^{106} during digestion and no significant counting error due to self-absorption. All samples were counted with an end-window Geiger tube. Unless otherwise noted, all results were corrected for radioactive decay.

EXPERIMENTS AND RESULTS

SINGLE DOSE GASTROINTESTINAL ABSORPTION STUDIES

Effect of pH. Ruthenium solutions of pH 1, 2, 4, and 6 ($\pm$0.05 pH unit) were intragastrically administered to 24 female rats, 6 rats per pH level. Approximately 15 μc Ru^{106} was administered to each rat. The animals were sacrificed after twenty-four hours, the pelt, feet, tail, and head discarded and the remainder of the animal analyzed. The results are shown in Table 1.

Total absorption was essentially the same at pH 1, 2, and 4, but definitely lower at pH 6. The distribution of ruthenium among the various organs and tissues is typical of that seen at a short time interval following ruthenium administration.

The value of approximately 0.75 per cent for ruthenium absorbed and retained for a twenty-four hour period is somewhat lower than the figure which we have usually obtained in twenty-four hour experiments with pH 2 solutions. Variation in absorption results by as much as a factor of two, between different experiments, has been quite typical, although agreement between animals in the same experiments is usually much better. This variability is quite possibly due to differences in the chemical

TABLE I

EFFECT OF pH ON GASTROINTESTINAL ABSORPTION OF RUTHENIUM
(AVERAGE VALUES FROM 6 RATS)

Tissue	Retention 24 Hours Post Feeding (per cent of dose/gm. tissue)			
	pH 1	pH 2	pH 4	pH 6
Kidney	.077	.11	.12	.017
Liver	.021	.025	.025	.0040
Ovaries	.0077	.0096	.0066	.0012
Spleen	.0048	.0074	.0057	.0014
Bone	.0037	.0046	.0044	.0013
Lungs	.0034	.0058	.0053	.0012
Heart	.0033	.0044	.0039	.0008
Fat	.0018	.0022	.0021	.0003
Muscle	.0014	.0016	.0020	.0004
Brain	.0003	.0003	.0003	.00009
Blood	.0050	.0066	.0066	.0014
Residual Carcass	.0022	.0029	.0029	.0007
Total Animal (% of dose ± standard deviation)	.66 ± .18	.75 ± .09	.78 ± .07	.14 ± .02

or physical state of ruthenium in the solutions fed.

Values for gastrointestinal absorption such as obtained in this experiment are, of course, not a true measure of total absorption, since absorption and excretion are occurring throughout the twenty-four hour experimental period. More precise values for total absorption were obtained from chronic feeding experiments.

Effect of Chemical State. Because of the complexity of ruthenium chemistry, concern was felt over the reproducibility of experiments employing ruthenium solutions which might differ in the proportion of valence states present, the extent of hydrolysis, or in some other subtle manner. In the experiments performed to evaluate this problem, no effort was made to explore thoroughly these various factors. The sole object was to determine whether major changes in the methods of solution preparation might significantly affect the absorption or distribution of the ruthenium in the animals to which these solutions were fed. By employing oxidizing and reducing agents, and aging the solutions for various time periods before feeding, it was hoped to obtain solutions which differed significantly in the chemical and physical properties of the contained ruthenium. The nature of these differences was not measured but can be estimated from what is known of the chemistry of ruthenium.

The six solutions employed are described in Table II. These solutions were fed, each to a group of 6 female rats, which were sacrificed and analyzed for Ru^{106} content after twenty-four hours. The pattern of ruthenium distribution was essentially the same for all solutions fed (Table II). There is an indication that total absorption may be affected by the method of solution preparation; however, this effect results in, at most, no more than a two-fold difference. The conclusion seems justified that the gastrointestinal absorption of ruthenium from pH 2 solutions is relatively insensitive to the ionic form, or valence state of the ruthenium contained.

Effect of Specific Activity of Ru^{106} Fed. The effect of Ru^{106} specific activity on gastrointestinal absorption was studied in an experiment in which nonradioactive ruthenium was added to the solutions fed, in amounts equal to 10, 100, and 1,000

TABLE II

EFFECT OF CHEMICAL AND PHYSICAL STATE ON GASTROINTESTINAL ABSORPTION OF RUTHENIUM
(AVERAGE VALUES FROM 6 RATS)

Solution Fed*	A	B	C	D	E	F
Ox. or Red. Agent	None	None	NaOCl	NaOCl	$SnCl_2$	$SnCl_2$
Aging of Solution	30 min.	6 da.	30 min.	6 da.	30 min.	6 da.
Probable Valence State	3 and 4	3 and 4	4	4 (?)	3	3 (?)
Probable Physical State	ionic	coll.	ionic	coll.	ionic	?
Tissue	Retention 24 Hours Post Feeding (per cent of dose/gm. tissue)					
Kidney	.19	.16	.20	.28	.12	.12
Liver	.041	.029	.038	.048	.026	.025
Spleen	.012	.008	.011	.015	.007	.007
Bone	.012	.008	.012	.014	.008	.008
Muscle	.004	.003	.004	.004	.002	.002
Residual Carcass	.005	.003	.005	.006	.003	.003
Total Animal (% of dose ± standard deviation)	1.3±.3	1.3±.4	1.0±.5	1.7±.7	1.1±.5	.86±.17

* pH of all solutions was 2.05±0.1.

times the total ruthenium content of the Oak Ridge "carrier free" solution. Six female rats were fed approximately 20 μc Ru^{106} at each concentration level, and sacrificed after twenty-four hours. There appeared to be no clearly significant effect of ruthenium concentration on either absorption or distribution (Table III).

Early Distribution of Absorbed Ru^{106} in Blood and Kidneys. Seventy-two female rats were given a single intragastric feeding of approximately 8 μc Ru^{106}, in 1 ml. of pH 2, chloride solution. The animals were starved for eighteen hours previous to the isotope administration. They were sacrificed in groups of 6 at intervals of thirty-five, seventy and one hundred and twenty-five minutes, and three, five, seven, ten,

TABLE III

EFFECT OF SPECIFIC ACTIVITY ON GASTROINTESTINAL ABSORPTION OF RUTHENIUM 106
(AVERAGE VALUES FROM 6 RATS)

Tissue	Retention 24 Hours Post Feeding (per cent of dose/gm. tissue)			
	Solution A .005 mg./20 μc	Solution B .05 mg./20 μc	Solution C .5 mg./20 μc	Solution D 5.0 mg./20 μc
Kidney	.17	.13	.087	.12
Liver	.035	.025	.019	.025
Spleen	.0099	.0076	.0049	.0063
Bone	.0097	.0058	.0040	.0054
Muscle	.0031	.0021	.0020	.0020
Residual Carcass	.0042	.0033	.0025	.0026
Total Animal (% of dose ± standard deviation)	1.28±.14	.79±.35	.62±.07	.72±.17

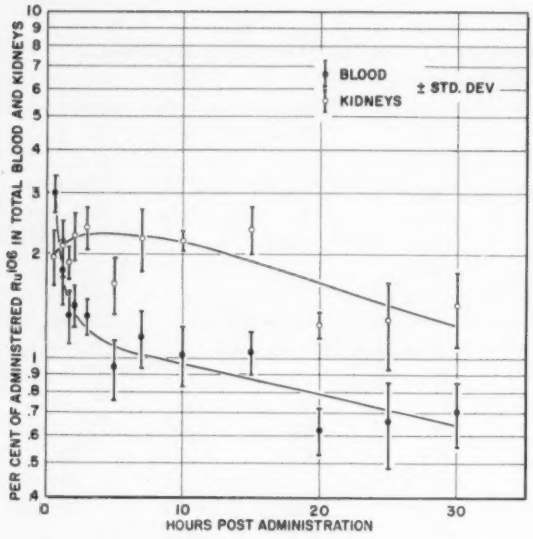

FIG. 1. Ru^{106} in blood and kidneys at intervals following intragastric administration.

fifteen, twenty, twenty-five, and thirty hours, post feeding. Kidneys and a blood sample were assayed for Ru^{106} content. Results are shown in Figure 1. These data were obtained incidental to an experiment performed to determine the time of passage of ruthenium through the gastrointestinal tract. A detailed account of the passage time data will be presented in a separate publication.

From the steep drop in blood Ru^{106} level during the interval from thirty-five to seventy minutes post administration it must be concluded that the bulk of ruthenium absorption occurred during the first thirty-five minutes, this despite the fact that over half of the administered Ru^{106} was still in the stomach at the thirty-five minute sacrifice. Apparently, regardless of its location in the gastrointestinal tract, significant absorption of ruthenium occurs only during a short time interval following ingestion. A reasonable explanation of this observation would be that the ruthenium, as administered, was in an absorbable state which, upon mixing with the contents of the gastrointestinal tract, was rapidly converted to a nonabsorbable state.

Total absorption in this experiment was considerably higher than that observed in chronic feeding experiments to be described later in this paper. Total Ru^{106} in blood and kidneys, thirty-five minutes after administration, amounted to about 5 per cent of the administered dose. An additional quantity of absorbed ruthenium is undoubtedly present in other tissues and in urine. This high absorption may possibly be attributed to the eighteen hour fasting period which preceded the intragastric administration. Such an explanation would appear quite plausible if, as postulated, absorption is limited by reactions which occur between the ruthenium and the contents of the tract.

The majority of absorbed ruthenium is apparently cleared from the blood with a half-life of not longer than thirty minutes. The latter portion of the blood retention curve exhibits a biologic half-life of about one day. Still longer half-life components are observed in longer-term retention studies to be described later.

After the initial build-up in the kidney, ruthenium is lost with an apparent half-life of about one day. Components with much longer half-lives are also present, as demonstrated in retention experiments of longer duration.

DISTRIBUTION AND RETENTION OF RUTHENIUM FOLLOWING INTRAPERITONEAL ADMINISTRATION

Thirty-six female rats, average weight 249 gm. were injected intraperitoneally with 7.7 μc of Ru^{106}. Groups of 4 animals were sacrificed at intervals of one, two, four, eight, sixteen, thirty-one, sixty-four, one hundred and twenty-eight, and two hundred and fifty-six days following injection. The results of ruthenium analyses of representative tissues are shown graphically in Figure 2. Data are expressed as percentage of injected dose per gram tissue and normalized to a 250 gm. rat.

Retention curves for all tissues analyzed were resolved into two or more exponential components. The biologic half-lives associated with these components are shown in Table IV. These half-lives should be considered as only approximations. Resolution of short-lived components from the re-

tention curves was complicated by the fact that during the first few days following injection, deposition of ruthenium in the tissues was proceeding concurrently with loss from the tissues. Thus, in the case of kidney, maximum ruthenium content was not attained until four days after injection, and the one day half-life component observed in the previously described experiment (Fig. 1) was completely masked.

While the hold-up of ruthenium in the peritoneal cavity was undoubtedly responsible for some apparent lengthening of the shorter half-lives measured, it probably did not significantly affect the longer half-lives. One day after injection, less than 3 per cent of the administered dose remained in the muscular tissue in the region of the peritoneal cavity, and at the later sacrifice periods the concentration of ruthenium in these tissues was comparable to that in the total residual carcass.

DISTRIBUTION AND RETENTION OF RUTHENIUM FOLLOWING CHRONIC INTRAGASTRIC ADMINISTRATION

Data were obtained on the retention of Ru^{106} over a period of one hundred and forty-nine days following a seventy-one day period of chronic feeding. The animals were fed approximately 1.8 μc of Ru^{106} by stomach tube, five days a week. The average daily dose, including week-ends was, therefore, about 1.3 μc. The animals were sacrificed in groups of 3–5, except for a single animal sacrificed at thirty days. Results of ruthenium analyses on representative tissues are shown graphically in Figure 3. Results are plotted as percentage of average daily dose per gram tissue and normalized to a 400 gm. rat. Retention curves for most of the tissues were fairly accurately represented by a single exponential function, or by the sum of two exponentials. Biologic half-lives derived from these exponential functions are listed for each tissue in Table v.

As would be expected, the longer-lived components are more prominent following chronic feeding, than following a single intraperitoneal injection (Table iv). The

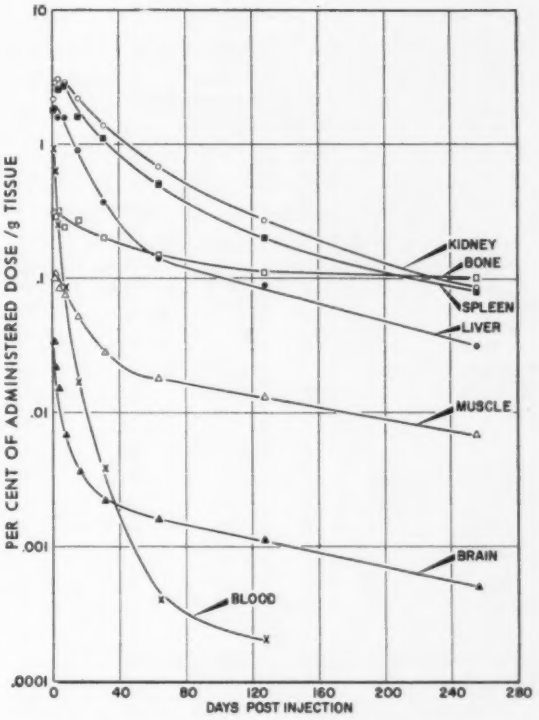

FIG. 2. Retention of Ru^{106} in representative tissues following intraperitoneal administration.

long-lived components accumulate ruthenium throughout the chronic feeding period, while the shorter-lived components soon attain an equilibrium level. A comparison of the results of the three retention experiments: (1) thirty hour retention period following single intragastric administration (Fig. 1), (2) two hundred and fifty-six day retention period following single intraperitoneal administration (Fig. 2 and Table iv), and (3) one hundred and forty-nine day retention period following chronic feeding (Fig. 3 and Table v) illustrates quite clearly the difficulties involved in describing the retention of an isotope in a given organ or tissue. The assumption of a single biologic half-life for Ru^{106} in most of the tissues studied would lead to a very crude approximation of the actual picture.

BUILD-UP OF RUTHENIUM IN TISSUES DURING CHRONIC FEEDING

Seventy-One Day Experiment. A total of 86 male rats, average weight 248 gm. at the

TABLE IV

BIOLOGIC HALF-LIVES FOR RUTHENIUM IN TISSUES AS DETERMINED FOLLOWING INTRAPERITONEAL INJECTION OF RUTHENIUM CHLORIDE SOLUTION

Tissue	Shorter-Lived Component		Longer-Lived Component	
	Fraction of Total Ruthenium	Half-Life (days)	Fraction of Total Ruthenium	Half-Life (days)
Kidney	.75	16	.25	80
Liver	.85	10	.15	80
Ovary	.75	13	.25	120
Spleen	.70*	17	.15	100
Bone	.50	15	.50	340
Lungs	.90	9	.10	100
Heart	.80	8	.20	100
Muscle	.80	9	.20	140
Brain	.35*	6	.06	120
Stomach	.70	8	.30	120
Small Intestine	.90	10	.10	140
Large Intestine	.90	8	.10	120
Residual Carcass	.75	10	.25	220

* Additional component of shorter half-life present but could not be resolved.

start of the experiment, was fed by stomach tube, 1.8 μc Ru^{106} per day, five days a week. The average daily dose, including week-ends, was 1.3 μc over the total seventy-one day period. Groups of 3 to 5 rats were sacrificed at intervals of one, ten, seventeen, twenty-four, thirty-one, fifty-two, and seventy-one days after initiation of feedings. Animals were sacrificed twenty-four hours after the last previous feeding, and except for the first group, after at least three consecutive days of feeding.

Results from the build-up phase of the experiment are shown in Table VI. Because of the marked increase in weight during the course of the experiment, results were normalized to a 400 gm. rat. While no other tissue approached the ruthenium concentration present in the kidney, it is significant that most tissues other than kidney appeared to be still increasing in ruthenium concentration at the end of the

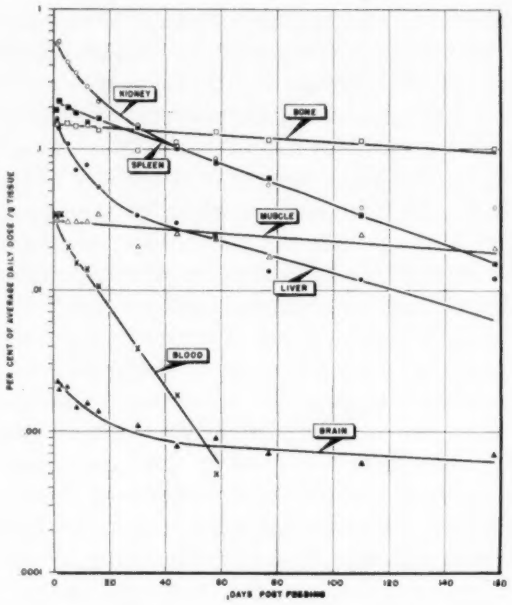

FIG. 3. Retention of Ru^{106} in representative tissues following chronic feeding.

seventy-one day feeding period. The concentration of ruthenium attained in bone is of particular interest, since it is, at the end of the feeding period, only a factor of about four times lower than the concentration in the kidney. Employing the conventional assumption that a radioisotope in

TABLE V

BIOLOGIC HALF-LIVES FOR RUTHENIUM IN TISSUES AS DETERMINED FOLLOWING CHRONIC RUTHENIUM FEEDING

Tissue	Shorter-Lived Component		Longer-Lived Component	
	Fraction of Total Ruthenium	Half-Life (days)	Fraction of Total Ruthenium	Half-Life (days)
Kidney	.65	5	.35	40
Liver	.70	6	.30	50
Testes	.20	?	.80	120
Spleen	0		1.0	40
Bone	0		1.0	250
Lungs	.30	?	.70	180
Heart	.30	?	.70	140
Fat	.60	10	.40	110
Muscle	0		1.0	250
Brain	.60	10	.40	250
Blood	.20	?	.80	12

TABLE VI

RUTHENIUM BUILD-UP IN TISSUES DURING CHRONIC FEEDING
71 DAY EXPERIMENT—MALES

Time on Feeding (da.)	1	10	17	24	31	52	71
Average Weight at Sacrifice (gm.)	220	263	288	308	310	376	402
Tissues	Ruthenium Concentration (per cent of average daily dose/gm. tissue—normalized to 400 gm. rat)						
Kidney	.088	.34	.47	.46	.57	.67	.57
Liver	.019	.078	.098	.10	.13	.15	.17
Testes	.0020	.013	.022	.023	.032	.043	.049
Spleen	.0053	.027	.047	.054	.089	.16	.19
Bone	.0067	.049	.066	.080	.088	.12	.15
Lungs	.0067	.028	.039	.032	.044	.063	.056
Heart	.0041	.018	.020	.028	.027	.043	.044
Fat	.0026	.011	.013	.017	.018	.018	.026
Muscle	.0020	.011	.013	.014	.022	.027	.032
Brain	.0003	.002	.001	.001	.002	.002	.002
Blood	.0049	.017	.022	.019	.025	.034	.034

bone is five times as hazardous as the same average concentration of the radioisotope in a soft tissue, one would conclude from these results that bone should be considered the "critical organ" for radiation hazard considerations.

Five Hundred Day Experiment. To extend the findings just presented, 60 male rats (average weight 484 gm.) and 60 female rats (average weight 247 gm.) were placed on drinking water containing 0.01 μc Ru^{106}/ml. Groups of animals were sacrificed after fifty, one hundred and twenty-five, two hundred, three hundred, four hundred and five hundred days of this chronic exposure. Results of tissue analyses are shown in Tables VII and VIII. The data are subject to limitations frequently en-

TABLE VII

RUTHENIUM BUILD-UP IN TISSUES DURING CHRONIC FEEDING
500 DAY EXPERIMENT—MALES

Time on Feeding (da.)	50	125	200	300	400
Number of Animals	8	8	5	8	3
Average Weight at Sacrifice (gm.)	545	528	507	495	400
Tissues	Ruthenium Concentration (per cent of average daily dose*/gm.)				
Kidneys	.29	.44	.37	.27	.42
Spleen	.082	.16	.14	.13	.15
Liver	.058	.088	.094	.078	.11
Testes	.024	.049	.051	.059	.11
Bone	.037	.057	.046	.058	.063
Lungs	.026	.055	.047	.055	.053
Heart	.025	.050	.047	.049	.068
Muscle	.015	.028	.032	.043	.069
Fat	.009	.016	.016	.017	.026
Brain	.004	.002	.003	.004	.004
Residual Carcass	.016	.036	.045	.057	.081

* Average daily dose=0.34 μc.

TABLE VIII

RUTHENIUM BUILD-UP IN TISSUES DURING CHRONIC FEEDING
500 DAY EXPERIMENT—FEMALES

Time on Feeding (da.)	50	125	200	300	400	500
Number of Animals	10	10	8	10	7	6
Average Weight at Sacrifice (gm.)	270	268	252	299	267	274
Tissues	Ruthenium Concentration (per cent of average daily dose*/gm.)					
Kidney	.69	.88	.85	.54	.68	.68
Spleen	.24	.38	.38	.24	.28	.27
Liver	.14	.16	.19	.12	.14	.14
Ovaries	.14	.16	.27	.27	.22	.25
Bone	.060	.088	.11	.10	.11	.12
Lungs	.059	.095	.12	.10	.093	.071
Heart	.044	.073	.085	.081	.079	.079
Muscle	.027	.053	.067	.082	.092	.099
Fat	.020	.024	.053	.024	.044	.043
Brain	.003	.004	.004	.004	.004	.004
Residual Carcass	.036	.070	.097	.088	.096	.098

* Average daily dose=0.27 μc.

countered in long term feeding experiments. The average daily doses employed in the calculations for Tables VII and VIII were not constant over the entire experimental period, nor were they constant between animals for any given portion of the experimental period. Estimates of the average daily dose were derived from data on the loss of weight from the water bottles and are undoubtedly somewhat higher than the actual average dose consumed, due to wastage. For this reason, no significance should be attached to the fact that higher ruthenium concentrations were attained in some tissues at the end of the seventy-one day experiment (Table VI) than after five hundred days of chronic feeding.

The data may also have been significantly influenced by a virus infection early in the experimental period which caused the death of a number of the male animals, but had little apparent effect on the females. Because of this epidemic the last males were sacrificed at four hundred days and only 3 nonrepresentative (low weight) animals constituted this group. The rather markedly increased ruthenium concentration in these four hundred day male animals is in all probability attributable to their subnormal weight.

Despite these limitations certain conclusions should still be valid. Beyond the two hundredth day there is no indication of a markedly increasing concentration of ruthenium in any tissue except muscle. The high ruthenium concentration in the kidneys is not approached by that in any other tissue. The concentration in kidney relative to that in bone is considerably higher than observed in the seventy-one day experiment, and would indicate that, in these animals, kidney rather than bone should be considered the critical organ. The relatively high concentration of ruthenium attained in the gonads, particularly in the ovaries, is of particular interest.

Effect of Age on Ruthenium Deposition in Bone. The ratio of ruthenium concentration in kidney and bone is a critical issue in hazard considerations. In the seventy-one day chronic feeding experiment, this ratio was less than 5, and bone was therefore indicated as the critical organ. In the five hundred day experiment this ratio was 6 or greater, and the kidney was the apparent critical organ. The differing results in these two experiments might reasonably be attributed to the age and growth rate of the animals employed. In the seventy-one day experiment the animals gained over 150 gm.

during the feeding period. In the five hundred day experiment, weights were relatively constant throughout the feeding period. To check on this possible influence of growth on bone deposition of ruthenium, 11 male and 11 female weanling rats were placed on a 0.01 μc Ru^{106}/ml. drinking water regimen. Groups of animals were sacrificed after seventy-seven and one hundred and fifty days of continuous exposure. Results of tissue analyses are shown in Table IX. Again interpretation is complicated by the changing animal weights and water intakes during the course of the experiment. Comparisons between tissue concentrations in a given group should be valid, however. The kidney to bone concentration ratios were 3.6 and 3.3 for males and females in the seventy-seven day groups, and 3.8 and 4.1 in the one hundred and fifty day groups. The increased relative deposition of ruthenium in the bones of these younger animals is clearly indicated by the fact that in three out of the four groups bone shows a higher ruthenium concentration than any tissue other than kidney.

TABLE IX

RUTHENIUM BUILD-UP IN TISSUES OF RATS FED Ru^{106} CHRONICALLY FROM WEANING

Sex	Male		Female	
Time on Feeding (da.)	77	150	77	150
Number of Animals	4	7	7	4
Average Weight at Sacrifice (gm.)	349	375	221	224
Average Daily Dose (μc)	.17	.23	.12	.18
Tissues	Ruthenium Concentration (per cent of average daily dose/gm.)			
Kidneys	.47	.30	.88	.62
Spleen	.085	.078	.22	.24
Liver	.081	.073	.16	.14
Testes—Ovaries	.027	.029	.15	.16
Bone	.13	.080	.27	.15
Lungs	.041	.030	.078	.059
Heart	.034	.026	.062	.056
Muscle	.024	.027	.042	.042
Fat	.011	.014	.028	.029
Brain	.005	.002	.006	.003
Residual Carcass	.035	.032	.066	.061

EXCRETION OF RUTHENIUM DURING AND FOLLOWING CHRONIC FEEDING

During and following the seventy-one day chronic feeding experiment previously described, daily urine and feces collections were made from 5 to 8 animals. These Ru^{106} excretion data are of particular interest because they give the best estimate for total gastrointestinal absorption.

The daily excretion of Ru^{106} in urine and feces during the feeding period showed marked decreases over each week end, when feedings were not given. To smooth out the curve, the excretion during the twenty-four hour periods following each feeding was averaged for each five consecutive days of feeding, and this "average daily value" plotted for each week. Excretion curves for the duration of the experiment are shown in Figure 4. Data, as plotted, were not corrected for radioactive decay.

Of primary interest, from the standpoint of calculating ruthenium absorption, is the ratio of urinary to fecal excretion. This ratio, during the latter three-fourths of the feeding period was quite constant at 0.024. Therefore, at least 2.4 per cent of the ruthenium fed was absorbed from the gastrointestinal tract (the very small fraction of the total ruthenium fed which is retained in the animal can be ignored in this calculation). An additional fraction of the ruthenium fed may have been absorbed and re-excreted via the feces. This fraction can be estimated from the ratio of urinary to fecal excretion following cessation of ruthenium feeding. Within ten days after feeding of the ruthenium was terminated, all unabsorbed ruthenium had apparently been cleared from the gastrointestinal tract, and from this time on, the ratio of urinary to fecal ruthenium excretion was quite constant at 4.0. Therefore, 20 per cent of absorbed ruthenium is excreted via the

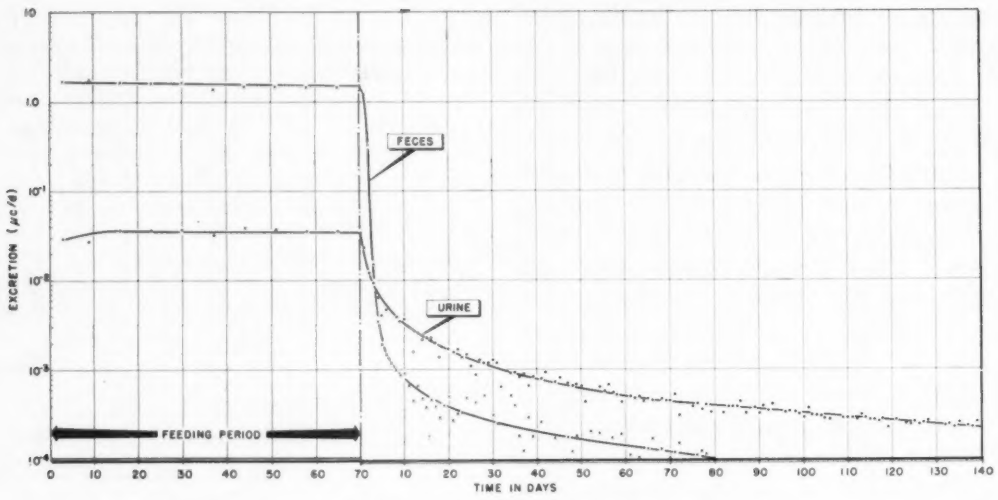

FIG. 4. Excretion of Ru^{106} during and following chronic feeding.

gastrointestinal tract, and the total absorption must be 25 per cent greater than that indicated by the ratio of ruthenium in urine and feces during the feeding period. This leads to a total absorption value of 3.0 per cent of the amount fed.

For the period from about seventy to one hundred and forty-nine days post feeding, the semilogarithmically plotted urinary excretion data (Fig. 4) are well fitted by a straight line. The slope of this line corresponds to a half-life of seventy days. Since these data were not corrected for radioactive decay, this is an "effective" half-life combining the effects of the three hundred and sixty-five day physical half-life of Ru^{106} and a biologic half-life of approximately eighty-five days for elimination of ruthenium from the animal.

EXCRETION OF RUTHENIUM FOLLOWING SINGLE ADMINISTRATION BY VARIOUS ROUTES

Groups of 4 or 5 female rats were administered a single dose of ruthenium, intragastrically, intravenously, intraperitoneally, or intratracheally. Urine and feces were collected daily and at sixty days the animals were sacrificed and tissues analyzed for ruthenium. Table x shows the distribution of ruthenium in the animal tissues plus a summary of total excretion from the four groups of animals for the sixty day period. All data are corrected for radioactive decay. Total recovery of ruthenium was satisfactory except in the intragastrically fed group, where over 40 per cent of the ruthenium was not accounted for. This unaccounted for ruthenium must have been missed in the early feces collections, since approximately 97 per cent of fed ruthenium is not absorbed. The urinary excretion of 2.7 per cent checks well with the value of 2.4 per cent obtained in chronic feeding experiments.

Total retention in the intravenous and intraperitoneal injection groups is very nearly the same. There are significant differences in the distribution, however. The lungs are notably high in the intravenous group, whereas most of the abdominal organs, and particularly abdominal fat, are significantly higher in the intraperitoneal group. These differences are what one might expect from the nature of the injections and the path taken by the ruthenium in the blood stream. The distribution of excreted ruthenium between urine and feces is virtually identical in the intravenous and intraperitoneal groups.

The intratracheally injected group differs in several notable respects from the intravenous group. The high fecal excretion indicates that a major portion of the in-

TABLE X

DISTRIBUTION OF RUTHENIUM IN THE RAT 60 DAYS AFTER ADMINISTRATION BY VARIOUS ROUTES (PER CENT OF ADMINISTERED DOSE/TISSUE)

Tissue	Intravenous	Intraperitoneal	Intragastric	Intratracheal
Kidney	.46	.98	.0085	.42
Liver	.59	1.30	.0085	.096
Ovaries	.018	.039	.00027	.0019
Spleen	.16	.32	.0024	.023
Bone	3.35	3.62	.066	.50
Lungs	.45	.10	.0016	1.50
Heart	.048	.047	.00076	.0052
Fat	.28	.91	.0066	.045
Muscle	3.87	2.54	.073	.54
Brain	.015	.001	.00005	.0005
Stomach	.098	.14	.0021	.019
Small Intestine	.22	.44	.0037	.036
Large Intestine	.18	.27	.0037	.040
Blood	.005	.010	.00039	.0070
Pelt	4.13	2.55	.109	1.09
Trachea				.19
Total Retained	13.9	13.3	.29	4.5
Excreted, Urine	53.8	51.8	2.7	28.8
Excreted, Feces	19.2	21.4	55.5	66.1
Total Accounted For	86.9	86.5	58.5	99.4

jected material was carried up the trachea and excreted via the gastrointestinal tract. Comparing urinary excretion in the two groups (intravenous and intratracheal) one would estimate that about half of the injected ruthenium was absorbed into the blood stream. However, the ruthenium content of most tissues in the intratracheal group was considerably less than half that of corresponding tissues in the intravenous group. Kidney is relatively very high in the intratracheal group. This may be due to the fact that absorption of ruthenium from the lungs continued at a relatively high rate throughout the experimental period, thus maintaining high ruthenium levels in this excretory organ. About 1.7 per cent of the injected dose remains in the lungs and trachea sixty days after administration.

Table XI shows the ruthenium concentration in the various tissues expressed as a percentage of the total retained dose. Expressed in this manner the essential similarity in distribution, following administration by various routes, is emphasized. Three significant differences between the four groups are apparent: (1) the higher concentration of ruthenium in the abdominal organs of the intraperitoneal injection group, (2) the high lung concentration in the intravenous injection group, and (3) the high kidney concentration in the intratracheal injection group.

The detailed excretion data are presented graphically in Figures 5 to 8. The logarithm of daily ruthenium excretion via urine and feces is plotted against time following administration. During the latter half of the experimental period the urine and feces curves are essentially parallel in all groups. During this period the ratio of ruthenium in urine to ruthenium in feces is about 5:1 following intraperitoneal and intragastric administration and about 3:1 following intravenous administration. These ratios compare with the 4:1 ratio observed in the previously discussed chronic feeding experiment. Following intratracheal injection the ratio of ruthenium in urine and feces during the latter portion of the experimental

TABLE XI

DISTRIBUTION OF RUTHENIUM IN THE RAT 60 DAYS AFTER ADMINISTRATION BY VARIOUS ROUTES (PER CENT OF RETAINED DOSE/GRAM TISSUE)

Tissue	Intravenous	Intraperitoneal	Intragastric	Intratracheal*
Kidney	2.0	4.4	1.8	9.0
Liver	.56	1.4	.41	.48
Ovaries	.94	2.3	.66	.97
Spleen	2.2	4.9	1.6	1.6
Bone	1.6	1.7	1.5	1.1
Lungs	2.6	.59	.45	—
Heart	.44	.42	.38	.24
Fat	.12	.40	.13	.090
Muscle	.24	.17	.23	.17
Brain	.007	.008	.010	.010
Stomach	.58	.90	.59	.59
Small Intestine	.35	.69	.28	.35
Large Intestine	.54	.90	.59	.62
Blood	.002	.005	.010	.014
Pelt	.71	.47	.93	1.0

* Per cent of retained dose exclusive of that in lungs and trachea.

period is only 2:1, and for the first fifteen days following injection fecal excretion of ruthenium exceeds urinary excretion. This is due, of course, to removal of ruthenium from the lungs via the bronchi, trachea, and gastrointestinal tract.

Beyond about the eighth day post injection, all of the excretion curves can be well fitted by equations consisting of two exponential terms. The slower component exhibits a biologic half-life of from sixteen to twenty days, except for the intratracheal group, where the half-life is 12.5 days. The shorter half-life in the intratracheal group is reasonable in view of the continued introduction of ruthenium from the unabsorbed reservoir in the lungs. The faster components in all groups exhibit half-lives of from 2.5 to 4.5 days. While these two exponential components for each group adequately describe the excretion over most of the time period studied, they account for only a small portion of the total ruthenium excreted. The bulk of ruthenium excretion occurs during the first few days after administration. Several of the excretion curves are much more satisfactorily represented as power functions of time. Table XII lists exponential and power function equations for each of the excretion curves, together with the time limits within which each equation is applicable. It is evident that the simpler power function provides a better description of the total results in many cases. It can also be predicted with confidence that excretion data beyond sixty days post administration would be reasonably well represented by the power functions listed, but would not be adequately represented by the exponential equations unless additional terms were added.

PERCUTANEOUS ABSORPTION STUDIES

A single experiment was performed comparing the absorption of ruthenium from 2.0 *N* and 0.01 *N* HCl solutions, after expo-

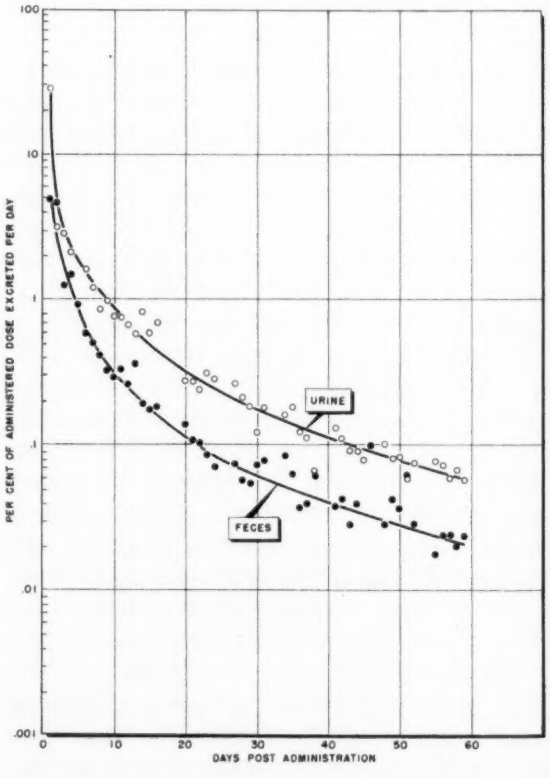

FIG. 5. Excretion of Ru^{106} following single intravenous injection. (Semilogarithmic plot.)

sure to the skin for one, five or twenty-four hours. Five animals were exposed in each group. The area to be contaminated on the right thigh was shaved a day prior to exposure. Ten microliters of the ruthenium solution, containing approximately 2 μc Ru^{106}, was spread over an area of 1 cm.^{2}. The contaminated areas were not covered during the exposure period.

At sacrifice, the exposed skin area and underlying tissue were removed for separate analysis. The remainder of the animal was dissected and the various tissues analyzed for ruthenium content. Results are shown in Table XIII.

The values listed as "total absorbed" do not include ruthenium in the gastrointestinal tract or pelt. The gastrointestinal tract will contain largely ruthenium ingested by the animal during the exposure period, and the pelt is likely to be grossly contaminated externally. It is obvious that the amount of ruthenium ingested, as indicated by the gastrointestinal tract analyses, could not have resulted in significant absorption, compared to the amount absorbed through the skin.

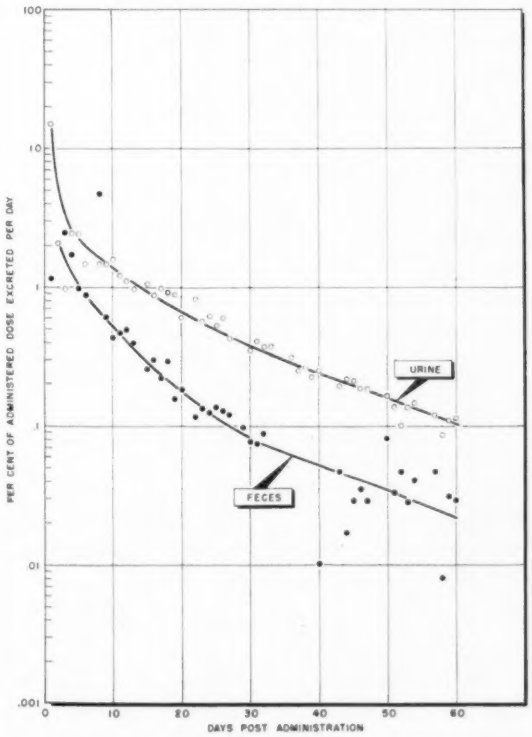

FIG. 6. Excretion of Ru^{106} following single intraperitoneal injection. (Semilogarithmic plot.)

The total recovery of ruthenium in the five and twenty-four hour exposure experiments was very poor. This is inevitable in experiments of this type. While the calculation of any exact absorption coefficients is precluded, the results are nonetheless of practical interest since the conditions of exposure closely simulate those to which humans might be subjected.

Total absorption is clearly a function of acidity and increases with increasing length of exposure. The distribution of the absorbed ruthenium among the various tissues is similar to that observed following other methods of administration, except for the much higher concentration of ruthenium in the exposed thigh. This is presumably due to absorbed ruthenium which has not yet found its way into the general circulation.

GENERAL DISCUSSION AND CONCLUSIONS

In this section we will confine ourselves to the consideration of internal exposure limits for Ru^{106}, and particularly to the derivation of a maximum permissible concentration (MPC) for Ru^{106} in drinking water. In the absence of human exposure data we will, of necessity, assume that the various organ uptake and retention values, as determined in the rat, apply to humans. We will also assume that our data, obtained for the most part from the administration of pH 2 solutions, is applicable to contaminated drinking water situations. In view of the approximately five-fold lower gastrointestinal absorption of ruthenium administered in near neutral solutions (Table I), the basing of calculations on results from pH 2 solutions may lead to somewhat conservative exposure limits.

For most radioisotopes maximum permissible concentrations have been derived from animal experiments involving a single administration of the radioisotope. The calculations conventionally employed[7,10] assume that a constant fraction of the ad-

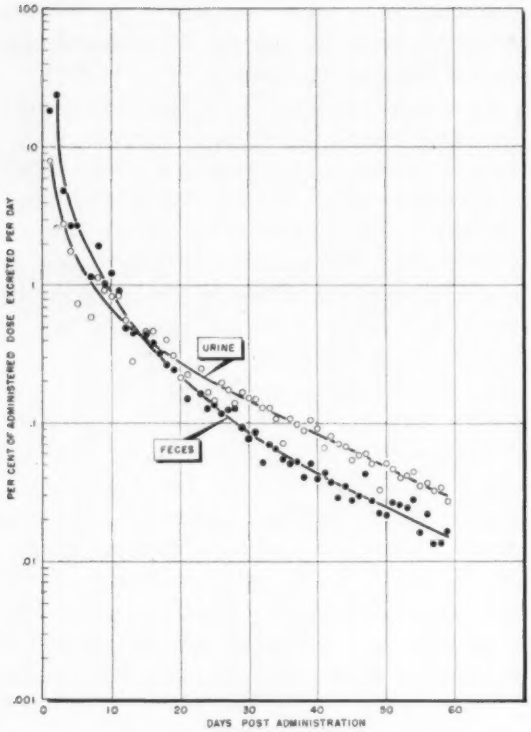

Fig. 7. Excretion of Ru^{106} following single intratracheal injection. (Semilogarithmic plot.)

ministered dose reaches the critical organ and that the isotope is lost from the critical organ at a rate which may be described by a single exponential function. Data from the present ruthenium studies are clearly inconsistent with these assumptions. The fraction of ingested Ru^{106} which reaches the bone is a function of age, major fractions of kidney ruthenium are lost with half-lives varying from one to at least eighty days, and, although most of the ruthenium which accumulates in the bone appears to be retained with a half-life of the order of several hundred days, such a half-life is not consistent with the leveling off of bone Ru^{106} content after one hundred to two hundred days of chronic feeding.

A more straightforward approach to the problem of permissible limits can be based on the results of chronic feeding studies. The actual concentration of the isotope in the critical organ may be determined after various periods of feeding. These values, in relation to the amount of isotope fed daily, lead directly to an evaluation of the maximum permissible concentration in ingested material.

The tissues of greatest concern are kidney, bone, and gonads. The fraction of daily ruthenium intake which accumulates in these organs after various periods of chronic feeding is shown in Table XIV. For none of these tissues does there appear to be any clearly significant increase in the level of ruthenium deposition beyond one hundred and twenty-five days on chronic feeding, although there is perhaps some indication of such a continuing increase in the case of bone in the female animals, and in the case of the testes. From the data it is not possible to conclude that a true equilibrium level has been attained in any of the tissues, and it is doubtful whether such an equilibrium should be expected. Cer-

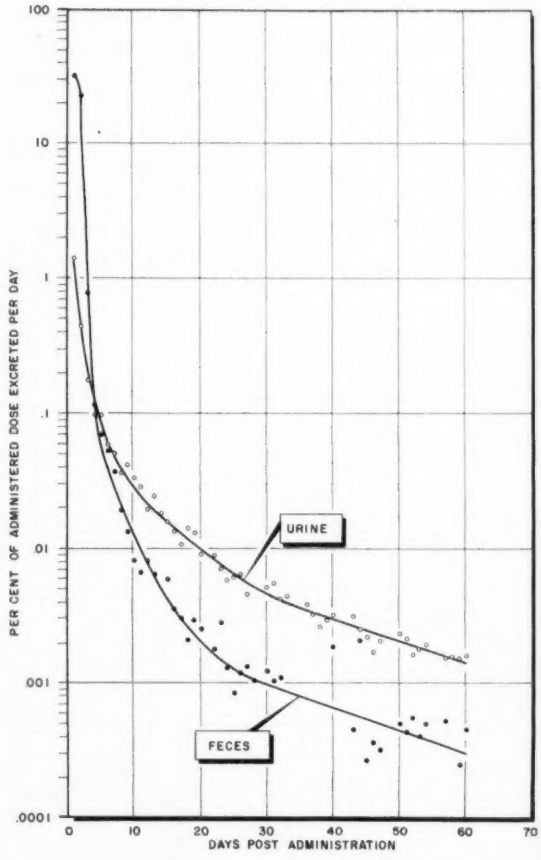

Fig. 8. Excretion of Ru^{106} following single intragastric feeding. (Semilogarithmic plot.)

TABLE XII

EQUATIONS FOR EXCRETION OF RUTHENIUM FOLLOWING ADMINISTRATION BY VARIOUS ROUTES

Route of Administration	Exponential Function*	Limits of Applicability	Power Function*	Limits of Applicability
Intravenous	$E_u = .036e^{-0.17t} + .0046e^{-0.035t}$ $E_f = .012e^{-0.18t} + .0016e^{-0.035t}$	$5 \leq t < 60$ $6 \leq t < 60$	$E_u = .29t^{-1.48}$ $E_f = .08t^{-1.42}$	$1 \leq t < 60$ $1 \leq t < 60$
Intraperitoneal	$E_u = .025e^{-0.15t} + .012e^{-0.041t}$ $E_f = .018e^{-0.17t} + .0030e^{-0.043t}$	$4 \leq t < 60$ $5 \leq t < 60$	$E_u = 1.7t^{-1.81}$ $E_f = .29t^{-1.71}$	$15 \leq t < 60$ $8 \leq t < 60$
Intratracheal	$E_u = .045e^{-0.29t} + .0075e^{-0.055t}$ $E_f = .050e^{-0.21t} + .0040e^{-0.055t}$	$4 \leq t < 60$ $8 \leq t < 60$	$E_u = .78t^{-1.88}$ $E_f = 1.2t^{-2.15}$	$8 \leq t < 60$ $2 \leq t < 60$
Intragastric	$E_u = .0010e^{-0.17t} + .00013e^{-0.036t}$ $E_f = .0020e^{-0.29t} + .00003e^{-0.038t}$	$8 \leq t < 60$ $7 \leq t < 60$	$E_u = .014t^{-1.64}$ $E_f = .0066t^{-1.82}$	$1 \leq t < 60$ $8 \leq t < 60$

* E_u = Fraction of administered dose excreted in urine per day, t days after dosage.
E_f = Fraction of administered dose excreted in feces per day, t days after dosage.

tainly in the case of bone, there can be no steady state equilibrium since the highest levels are recorded in the young animals. Regardless of the reasons for the fluctuations in ruthenium level, these data cover a major fraction of the life span of the rat, and representative values may be chosen for each tissue. These representative values for fraction of daily intake in kidney, bone, and gonads are listed as item (B) in Table XV. The values for kidney and gonads are quite straightforwardly derived from the data. In the case of bone, the higher values obtained in the rats fed from weaning were more heavily weighted.

Table XV summarizes the calculations of human maximum permissible concentrations for Ru^{106} in water, assuming various organs to be critical, and based on a permissible chronic dose of 300 mrem/week to the critical organ. These calculations are based on organ ruthenium content and no consideration is given to the gamma contribution from other tissues. An effective energy of 1.4 mev. is assumed for Ru^{106}-Rh^{106} in all of the organs, regardless of their dimensions. Errors introduced by these assumptions are certainly small compared to those inherent in the extrapolation of rat results to man. On the basis of these calculations, testes are the critical organs. Although testes accumulate a lower Ru^{106} concentration than either kidney or ovaries in the rat, the extrapolation to man of "fraction of intake deposited per organ" results in a higher apparent concentration in human testes, because of the much smaller mass of testes relative to most other organs in man as compared to the rat. For similar reasons, the calculations of Table XV result in bone appearing less critical than kidney in man, whereas it is more critical than kidney in the rat.

In view of the difficulties involved in extrapolating from rat to man, the unequivocal choice of a critical organ is impossible. Considering all of the data, a value of 4×10^{-3} μc/ml. for the maximum permissible concentration in water would appear to be a reasonable choice. For comparison the present recommended value for the maximum permissible concentration in water is 0.1 μc/ml.[7,10] This much higher value is based on an estimated absorption from the gastrointestinal tract of less than 0.05 per cent, a much lower absorption than was measured in the present study.

Another approach to the calculation of a

TABLE XIII

ABSORPTION OF RUTHENIUM CHLORIDE THROUGH THE SKIN OF RATS
(AVERAGE VALUES FROM 5 ANIMALS)

Tissue Assayed	Per Cent of Administered Dose/Tissue					
	2.0 *N* HCl Solution			0.01 *N* HCl Solution		
	1 hr.	5 hr.	24 hr.	1 hr.	5 hr.	24 hr.
Kidney	.070	.32	.55	.0035	.026	.058
Liver	.11	.27	.66	.0048	.028	.051
Ovaries	.0012	.0042	.061	.0002	.0003	.0003
Spleen	.0027	.0090	.032	.0003	.0002	.0016
Bone	.050	.13	.13	.0059	.010	.019
Lungs	.014	.052	.055	.0006	.0082	.0053
Heart	.0047	.011	.021	.0002	.0010	.0009
Fat	.030	.12	.18	.0020	.027	.025
Muscle	.18	.38	.85	.018	.17	.13
Brain	.0012	.0040	.0049	.0001	.0008	.0004
Blood	.18	.57	.79	.0051	.033	.041
Exposed Thigh	.29	.64	.89	.0031	.043	.061
Total Absorbed	.93	2.51	4.22	.044	.35	.49
Gastrointestinal Tract and Contents	.66	1.90	.92	.0005	.24	.88
Pelt	.18	.62	.77	.021	.30	.26
Exposure Area	97.	46.	49.	84.	88.	15.
Total Recovery	99.	51.	55.	84.	89.	17.

maximum permissible concentration may be made by comparing Ru^{106} with Ra^{226}. The permissible burden for Ra^{226} in bone, based upon human exposure experience, is 0.1 μc.[7] Comparative toxicity studies in mice have indicated that, per μc injected, Ra^{226} is about 5 times as toxic as Ru^{106} at dosage levels resulting in median survival times of as long as one hundred and fifty days.[2] Comparing published values of radium distribution from blood to bone with data on ruthenium from the present experiments it appears that only half as large a fraction of injected Ru^{106} will reach the

TABLE XIV

FRACTION OF DAILY RUTHENIUM INTAKE PRESENT IN KIDNEY, BONE, AND GONADS AFTER VARIOUS PERIODS OF CHRONIC FEEDING

Experiment	Duration of Feeding (da.)	Kidney		Bone		Gonads	
		Male	Female	Male	Female	Male	Female
Animals Fed after Attaining Maturity	50	.010	.014	.014	.013	.0014	.00020
	125	.015	.017	.021	.016	.0025	.00020
	200	.011	.015	.014	.017	.0024	.00019
	300	.009	.010	.019	.018	.0032	.00016
	400	.011	.014	.014	.019	.0030	.00019
	500		.014		.021		.00015
Animals Fed from Weaning	77	.011	.012	.028	.037	.0011	.00013
	150	.007	.009	.019	.021	.0013	.00012

TABLE XV

CALCULATION OF MAXIMUM PERMISSIBLE CONCENTRATION OF Ru^{106} IN WATER, BASED ON PERMISSIBLE DOSE OF 300 MREM/WEEK TO CRITICAL ORGAN

A. Critical Organ	Kidney	Bone	Testes	Ovaries
B. Fraction of Daily Intake in Critical Organ[a]	.015	.030	.003	.0002
C. Weight of Critical Organ in Human (gm.)[b]	300	7,000	40	8
D. Permissible Organ Burden (μc)[c]	.18	.84	.024	.005
E. Permissible Daily Intake (μc)[d]	12	28	8	25
F. MPC in Water (μc/ml.)[e]	.005	.013	.004	.011

[a] Best value from Table XIV.
[b] Values for kidney, bone and testes taken from Reference 7, for standard 70 kg. man.
[c] Number of μc in critical organ which will irradiate organ at a rate of 300 mrem per week. Calculated from formula:

$$Q = \frac{8.4 \times 10^{-4} W}{EN}$$

where: W = weight of organ in grams
E = effective energy (1.4 mev. for Ru^{106}-Rh^{106})
N = nonuniform distribution factor which is 5 for bone and unity for other organs.
[d] D/B.
[e] E/2,200 ml.[7]

bone as is the case with injected Ra^{226}. On the basis of bone deposited isotope, Ra^{226} is therefore only 2.5 times as toxic as Ru^{106}. In man Ra^{226} is generally presumed to produce 3 times the irradiation produced in the mouse due to retention in the bone of about 55 per cent of its daughter Rn^{222}, essentially all of which is lost from the much smaller, more rapidly metabolizing mouse. In the human, bone deposited Ra^{226} should therefore be 7.5 times as toxic as Ru^{106}. Based on present Ra^{226} limits the permissible burden of Ru^{106} in bone would, therefore, be .75 μc, which corresponds to a daily intake of 25 μc and maximum permissible concentration in water of .011 μc. Based on the two commonly employed methods for estimating maximum permissible concentrations, the values for bone as the critical organ are, therefore, in excellent agreement at about .01 μc/ml.

A much lower maximum permissible concentration for water than any of those calculated in Table XV would be required if the radiation dose to the lower large intestine is to be limited to 0.3 rem per week. From the standpoint of intestinal radiation a negligible amount of ingested ruthenium is removed from the gastrointestinal tract by absorption, and the dose to the intestine is determined only by the physical constants of the isotope, the rate of passage through the intestine and the dilution of the isotope by intestinal contents. Using estimates for these various parameters in the human, the International Commission on Radiological Protection (ICRP) calculates a maximum permissible concentration for water of 1×10^{-4} μc/ml.[7]

An even lower maximum permissible concentration for water might be required if more stringent limits are placed upon gonad irradiation, as suggested by the Committee on Genetic Effects of Atomic Radiation of the National Academy of Sciences.[6] Their recommendation of a limit for general population exposure of 10 r to the gonads during the first thirty years of life would result in a permissible dose of about 0.004 r/week from internally deposited radioisotopes which would reduce the maximum permissible concentration as calculated for testes in Table XV to a value of about 5×10^{-5} μc/ml.

SUMMARY

The metabolism of ruthenium in the rat was studied in experiments involving the

acute and chronic administration of Ru^{106} by various routes. Gastrointestinal absorption amounts to about 3 per cent of ruthenium fed as solutions in the pH range from 1 to 4, and is little affected by the chemical state or previous history of the solutions or by the concentration of ruthenium. The highest concentration of ruthenium, even after prolonged chronic feeding, is present in the kidney. Bone and gonads also accumulate sufficient concentrations of ruthenium to make them of comparable hazard concern to the kidney. Because of uncertainties inherent in the extrapolation of the rat data to man, an unequivocal choice of critical organ among these three possibilities cannot be made. Based on a permissible dose to the critical organ of 0.3 rem /week, the maximum permissible concentration for Ru^{106} in water is calculated to be 4×10^{-3} μc/ml. This would be approximately correct on the assumption of either kidney, bone, or gonads as critical organ. Limiting irradiation of the gastrointestinal tract itself to 0.3 rem/week results in a lower maximum permissible concentration of 1×10^{-4} μc/ml. Applying a genetic limit of 10 r to the gonads during the first thirty years of life results in a maximum permissible concentration of 5×10^{-5} μc/ml.

Biology Operation
Hanford Laboratories
General Electric Company
Richland, Washington

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ERYTHROCYTE SURVIVAL IN LEUKEMIA, HODGKIN'S DISEASE AND MALIGNANT LYMPHOMA AS DETERMINED BY RADIOCHROMATE*

By RONALD E. WAGGENER, M.D., PH.D., PEYTON T. PRATT, M.D., *and* HOWARD B. HUNT, M.A., M.D.
OMAHA, NEBRASKA

ANEMIA is commonly a major problem in patients with leukemia, Hodgkin's disease or malignant lymphoma. The pathogenesis of such anemia may relate to defective hematopoiesis, blood loss or shortened red blood cell survival. Blood loss may contribute to the anemia of patients with defects of the clotting mechanism such as occur in acute and terminal leukemia or with ulcerating lesions as in malignant lymphomas of the gastrointestinal tract. Hematopoiesis may be restricted by marrow replacement, by metabolic dysfunction or toxic depression of the marrow. In many cases the severity of the anemia occurring in patients with leukemia or malignant lymphoma is not fully accounted for by blood loss or suppressed hematopoiesis.

The role of reduced survival of erythrocytes in the anemia of leukemia and malignant lymphoma is not readily obvious and requires special studies for its detection and evaluation. No intrinsic abnormalities of red blood cells in these diseases have been identified[4] to suggest a cause for accelerated destruction of erythrocytes. Methods for determining survival of erythrocytes used in the past include the differential agglutination method,[1] studies of bile pigment metabolism,[10,15] studies of reticulocyte production,[2,3,12,13] and transfusions of foreign erythrocytes. The simplest and most reliable test for determining life span of erythrocytes is that based on the findings of Gray and Sterling,[8,9] using sodium radiochromate as a red blood cell tagging agent.

TECHNIQUE

In this investigation the sodium radiochromate method along with reticulocyte counts and bile pigment studies were used to study red blood cell survival and hematopoiesis. The tagging of red blood cells was carried out in silicone lined rubber stoppered bottles (Abbott Laboratories) containing a special A.C.D. anticoagulant. Twenty milliliters of blood were withdrawn from the patient and injected into a bottle containing 200 microcuries of sodium radiochromate (Rachromate, Abbott). The blood was incubated with this mixture at room temperature for twenty minutes with frequent gentle agitation. One hundred milligrams of ascorbic acid solution were then added (to stop the tagging process by chemical reduction of chromate) following which the labeled blood was re-injected into a vein of the patient. Blood samples of 10 ml. were then withdrawn at intervals of two to seven days over a period sufficiently long to assure valid results, five to fifteen samples being taken from each patient. The blood was centrifuged and quantitative radioactivity of the packed red cells determined in a well type scintillation counter. The results were corrected to counts per minute per milliliter of packed red blood cells, taking into account physical decay and the volume efficiency of the counter. Results were plotted on a semilogarithmic graph against time in days. Erythrocyte half survival time was then determined from the graph.

* From the Departments of Radiology and Hematology, University of Nebraska and Nebraska Methodist Hospitals, Omaha, Nebraska. Read by title at the Thirty-ninth Annual Meeting of the American Radium Society, Quebec City, Quebec, Canada, May 29–June 1, 1957.

This investigation was conducted by Dr. Ronald E. Waggener, Clinical Fellow of the American Cancer Society and sponsored by a grant from the American Cancer Society, Nebraska Division.

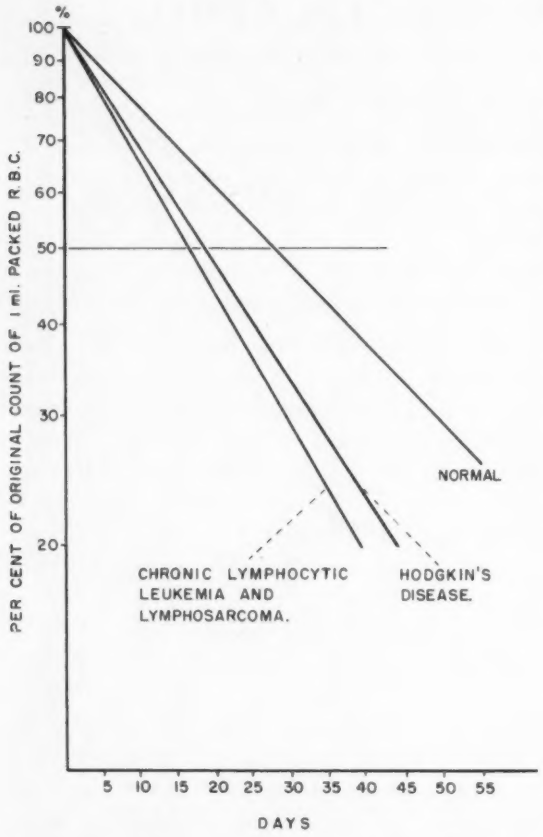

FIG. 1. Comparative average erythrocyte half survival time in normal controls and patients with leukemia, Hodgkin's disease and lymphosarcoma.

MATERIAL

Eight unselected cases of chronic lymphocytic leukemia, 2 of acute leukemia, 5 of Hodgkin's disease, 4 of lymphosarcoma, 1 of giant follicular lymphoma and 7 normal controls were studied. In addition to determination of red blood cell half survival time, all patients had frequent routine blood counts and 16 had periodic reticulocyte counts. Bile pigment determinations were carried out in 12 cases.

ERYTHROCYTE HALF SURVIVAL TIME

The average erythrocyte half survival time in a group of 7 normal people was twenty-eight days (Fig. 1) with a range of twenty-five to thirty-five days. This agrees well with the reports in the literature which indicate that the red blood cell half survival time by the sodium radiochromate method is twenty-five to forty days.[7,10,14,17] Actual total erythrocyte survival time is approximately one hundred and twenty days. Half time erythrocyte survival would therefore be expected to be sixty days, but because of elution of chromium from the circulating red blood cells the figure actually yielded by the sodium chromate method is approximately thirty-two days. Therefore, radiochromate half survival time provides a valid comparative index, being roughly 50 per cent of the actual half survival time.

All 8 patients with chronic lymphocytic leukemia had shortened red blood cell half survival times ranging from five to twenty-four days, the average for the group being 16.5 days which is one-half the average normal value by this method of thirty-two days. Reticulocyte counts were carried out on 6 of the patients with 4 showing normal levels under 1 per cent and 2 elevated levels of 3.5 and 2.1 per cent. Bile pigment studies carried out on 3 patients were all normal. Two of the 8 patients had no splenomegaly and yet erythrocyte survival time was reduced to twenty-three and eight days. These findings are summarized in Table 1.

The 2 patients with acute leukemia (one

TABLE I

SUMMARY OF FINDINGS ON PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Patient	Red Blood Cell Half Survival Time in Days	Average Hemoglobin in Gm.	Average Reticulocyte Count in Per Cent	Spleen—Cm. Below Costal Margin
1	18	13.6	—	6
2	12	9.3	0.8	10
3	22	11.9	0.9	12
4	23	10.5	0.8	Not palpable
5	8	9.9	3.5	Not palpable
6	5	9.0	2.1	12
7	20	8.1	—	3
8	24	10.2	0.2	3
Average	16.5	10.3		

granulocytic, the other lymphocytic) showed shortened erythrocyte half survival times of seventeen and fourteen days. The reticulocyte count in 1 patient was elevated to 5 per cent and was normal in the other. Neither patient had splenomegaly. Bile pigment studies did not detect any increased hemolysis in the 1 case studied.

All 5 patients with Hodgkin's disease showed increased destruction of erythrocytes. The range of half survival time was fifteen to twenty-three days and averaged nineteen days (59 per cent of normal). All the patients were anemic. Reticulocyte counts were slightly elevated on the 4 patients tested, the range being from 1.2 to 2.5 per cent. Bile pigment studies were carried out on 4 and all findings were normal. Only 1 patient had clinical evidence of splenomegaly. This was the patient with the longest erythrocyte half survival time in the group (twenty-three days). These results are summarized in Table II.

The patient with giant follicular lymphoma had minimal cervical lymph adenopathy of 1.0 to 1.5 cm. and appeared to be in good health with no anemia. The spleen was not palpable. In spite of these findings his erythrocyte half survival time was only nineteen days (60 per cent of normal).

Four patients with lymphosarcoma showed increased erythrocyte destruction. The half survival times ranged from seven to twenty-two days with an average of seventeen days (53 per cent of normal). Three of the 4 were anemic. The nonanemic patient had an erythrocyte half survival time of seventeen days, a normal reticulocyte level (0.5 per cent) with normal bile pigment studies and a nonpalpable spleen. The other 3 patients with anemia had splenomegaly. Two had elevated reticulocyte levels of 2.3 and 3.0 per cent. Bile pigment studies on all were normal. These results are summarized in Table III. In Case 19a, roentgen therapy was being delivered to the trunk during the initial determination of red blood cell survival time. Four months after therapy a further determination was carried out, represented in Table III as Case 19b. It will be noted that the shortened red blood cell survival time of seven days improved to a normal level of twenty-nine days four months after the course of roentgen therapy which amounted to a total of 90 r (air) whole trunk irradiation in a period of fifteen days. The enlarged spleen extending 14 cm. below the costal margin did not change significantly throughout this period.

Although data to be published by us elsewhere established that erythrocyte destruction can be accelerated by roentgen therapy, only a slight indication of such phenomenon can be detected in this group of patients. The number of patients and the differences noted are inadequate for definitive statistical analysis, but the comparative erythrocyte survivals between those receiving no therapy (average nineteen days) and those receiving roentgen

TABLE II

SUMMARY OF FINDINGS ON PATIENTS WITH HODGKIN'S DISEASE

Patient	Red Blood Cell Half Survival Time in Days	Average Hemoglobin in Gm.	Average Reticulocyte Count in Per Cent	Bile Pigment Studies	Spleen—Cm. Below Costal Margin
11	15	11.5	—	—	Not palpable
12	19	9.0	2.5	Normal	Not palpable
13	19	6.5	1.5	Normal	Not palpable
14	18	9.8	1.2	Normal	Not palpable
15	23	10.6	1.5	Normal	2
Average	19	9.5			

TABLE III

SUMMARY OF FINDINGS ON PATIENTS WITH LYMPHOSARCOMA

Patient	Red Blood Cell Half Survival Time in Days	Average Hemoglobin in Gm.	Average Reticulocyte Count in Per Cent	Bile Pigment Studies	Spleen—Cm. below Costal Margin
16	17	15.2	0.5	Normal	Not palpable
17	22	11.9	0.9	Normal	12
18	22	11.5	2.3	Normal	2
19a	7	10.8	3.0	Normal	14
19b	29	9.4	5.0	Normal	12

treatment (average sixteen days) are noteworthy. In leukemia, Hodgkin's disease or malignant lymphoma the average erythrocyte half survival time of the cases receiving irradiation during study was slightly shorter. Nitrogen mustard had no obvious effect on half survival time (eighteen days) in the 2 patients tested.

A thorough review of the literature revealed that other investigators using the Ashby technique,[4,5,6,16] had reported comparable shortening of erythrocyte survival in patients with leukemia or lymphoma. Böttner and Schlegel[5] reported a correlation between the degree of anemia and the decrease in the red blood cell survival time using the Ashby method in a group of patients with leukemia or malignant lymphoma.

RETICULOCYTE COUNT

Reticulocyte counts were carried out in 16 of the 20 cases studied and were elevated in 9. In 7 cases the red blood cell survival time was shortened in spite of a normal reticulocyte count. In those cases with markedly shortened erythrocyte survival (*i.e.*, less than ten days), the reticulocyte count was elevated above 1 per cent. The red blood cell survival time determination was found to be a more sensitive index of red blood cell destruction than the reticulocyte count. A reticulocyte count of 2 per cent or over suggests an accelerated release of erythrocytes from the marrow compensatory for an increasing rate of red blood cell destruction but may result also from blood loss or vitamin B_{12} therapy as in patients with pernicious anemia. Counts under 2 per cent were not correlated with red blood cell survival time.

BILE PIGMENT STUDY

Bile pigment studies consisting of serum bilirubin and urobilinogen (urinary and/or fecal) were conducted in 12 cases. Such studies did not indicate accelerated red blood cell destruction in any of these cases although sodium radiochromate studies indicated shortened red blood cell survival in all diseased patients tested.

SPLENOMEGALY

Berlin[4] reported a high incidence of splenomegaly in association with anemia in patients with leukemia. In our series only 6 of the 8 patients with chronic lymphocytic leukemia and decreased erythrocyte survival had palpable splenomegaly. Furthermore, the 2 patients with acute leukemia both had shortened erythrocyte survival but neither had evidence of splenomegaly. Of the 10 patients with malignant lymphoma, all presented decreased erythrocyte survival, but only 6 had palpable spleens. The average erythrocyte half survival time in 8 patients with nonpalpable spleens was 16.9 days and in 12 patients with enlarged spleens was 17.5 days indicating no consistent correlation between splenomegaly and reduced red blood cell survival. In other words, red blood cell survival can be anticipated to be reduced in leukemia and malignant lymphoma independent of splenomegaly. This would be particularly true in cases of acute leukemia

wherein the spleen is not commonly enlarged.

SUMMARY

1. Eight patients with chronic lymphocytic leukemia and 2 with acute leukemia were anemic and showed an erythrocyte half survival time only 50 per cent of normal.

2. The erythrocyte half survival time was shortened in 5 patients with Hodgkin's disease (59 per cent of normal), 4 with lymphosarcoma (53 per cent of normal), and 1 with giant follicular lymphoma (60 per cent of normal).

3. The reticulocyte count did not disclose mild destruction of red blood cells but was elevated in cases with more rapid destruction (*i.e.*, erythrocyte half survival time of ten days or less). Elevation of the reticulocyte count above 2 per cent would suggest accelerated destruction of red blood cells.

4. Bile pigment studies failed to reveal the accelerated red blood cell destruction indicated by sodium radiochromate in all 12 patients studied.

5. Reduced red blood cell survival time occurred without evidence of palpable splenomegaly in one-half of all cases.

6. Patients receiving roentgen therapy showed slightly shorter average erythrocyte survival than cases receiving no roentgen therapy while under study.

7. Four months following roentgen therapy, the red blood cell survival time in 1 patient with generalized lymphosarcomatosis had improved from a seriously low index (seven days) to a normal index (twenty-nine days).

Ronald E. Waggener, M.D.
University of Nebraska College of Medicine
42 and Dewey Avenue
Omaha 5, Nebraska

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ERYTHROCYTE SURVIVAL IN RABBITS AFTER SUBLETHAL TOTAL BODY IRRADIATION*

By RONALD E. WAGGENER, M.D., PH.D.,† *and* HOWARD B. HUNT, M.D.‡
OMAHA, NEBRASKA

IT IS generally accepted that ionizing radiation can produce anemia through depression of hematopoiesis[6,8] and rarely through induction of a hemorrhagic state.[10] According to Jacobson, Marks and Lorenz[4] doses below 100 r total body irradiation to rabbits caused no reduction in reticulocytes to indicate suppression of hematopoiesis, but a progressive reduction occurred with higher doses up to 1,000 r. Anemia was seen rarely in rabbits with doses below 500 r total body irradiation but became more frequent with progressively increasing doses. Hemorrhage occurs only with marked thrombocytopenia due to severe damage to the hematopoietic system from doses in the LD_{50} range. Acceleration of erythrocyte destruction by irradiation seems to deserve further investigation as a potential factor contributing to post irradiation anemia.

Accumulations of hemosiderin pigment indicating increased red blood cell destruction have been demonstrated histologically in the reticuloendothelial tissues of albino rats after injection of 4.5 μc of P^{32} per gram in the peritoneal cavity (Fig. 1).[7] Increased excretion of bile pigment after large doses of irradiation implies accelerated red blood cell destruction.[5] It has been noted that a large influx of red blood cells into the lymph and tissue spaces may occur after heavy irradiation, presumably because of damage to capillary walls.[1,5] Evidence drawn from the literature has stressed that near lethal doses of radiation may lead to increased destruction of erythrocytes.[1,5] The present investigation was undertaken to study the effect of relatively smaller doses of irradiation on red blood cell survival.

Twelve normal young adult rabbits of both sexes were injected intravenously with high specific activity $Na_2Cr^{51}O_4$, each animal receiving 10 μc. One milliliter samples of blood were removed by cardiac puncture once a week over a period of forty-nine days. Hematocrit values (micro method) and radioactivity determinations on packed erythrocytes were carried out. The latter values were corrected to counts per minute per milliliter of packed red blood cells, taking into account physical decay of the Cr^{51} and the volume efficiency of the scintillation detector used. No correction was applied for elution of radiochromium from erythrocytes. Levels of radioactivity were plotted on the logarithmic scale of semilogarithmic graph paper against time in days. The elapsed time period required for the corrected level of radioactivity to decrease to one-half (relative erythrocyte half survival time) averaged fifteen days with a range of eleven to twenty-three days. A twelve day value using the Cr^{51} method in rabbits has been previously reported.[3] Correction for elution would have given a hypothetic erythrocyte half survival time of about thirty days for the rabbits in our series.

Hematocrit determinations on the 5 rabbits tested showed no significant change, indicating that the weekly 1 ml. blood samples did not cause anemia during the period of observation as shown in Table 1.

A second group of 12 rabbits was prepared for study by incubating 3 to 5 ml. of blood from each rabbit with 100 μc of $Na_2Cr^{51}O_4$ in 1 to 3 ml. of special A.C.D. anticoagulant (Abbott Laboratories). The blood tagged by chromium was then reinjected intravenously. Normal relative eryth-

* From the Department of Radiology, University of Nebraska College of Medicine, Omaha, Nebraska.
This investigation was sponsored by a research grant from the Nebraska Auxiliary of the Veterans of Foreign Wars.
† Clinical Fellow in Radiology, American Cancer Society.
‡ Chairman and Professor of Radiology.

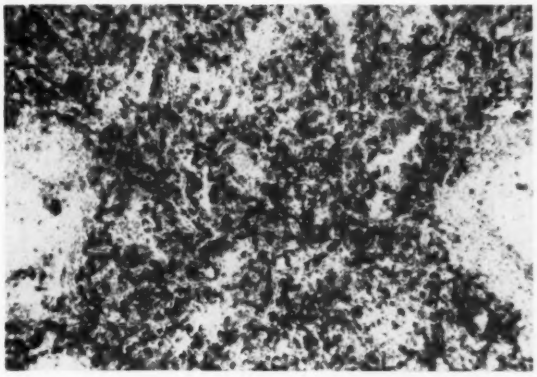

Fig. 1. Hemosiderin stain of rat spleen showing massive deposition in the red pulp fifteen days after the intraperitoneal injection of 4.5 μc of P^{32} per gram (×95.5).

rocyte half survival time was determined as before and found to average fifteen days with a range of nine to twenty-one days. It will be noted that the average normal erythrocyte half survival time was not altered by the 100 μc dose of $Na_2Cr^{51}O_4$ as compared with the 10 μc dose.

The group was then subjected to total body roentgen irradiation in ten daily treatments. The factors were 220 kv. const., Thoraeus II filter (half-value layer 2 mm. of copper), 20 ma., 2 meters distance at 2.8 r (air) per minute for eight minutes or 22 r per day for ten treatments to a total dose of 220 r in air or approximately 200 rads average tissue dose. The mean lethal dose of radiation in rabbits is about 1,000 r,[5] and the LD_{50} dose in thirty days is about 800 r.[4] Subsequently, serial determinations of radioactivity of packed red blood cells were carried out in an attempt to note any possible change induced by the irradiation. The average erythrocyte half survival time of the 11 survivors after irradiation was reduced to 7.5 days (Fig. 2) with a range of five to twelve days. One rabbit died from anesthesia. The total time of study extended to fifty-six days.

Evidence from the literature supports the above observations that irradiation can cause accelerated distintegration of erythrocytes.[1,5] Latta and Waggener[7] have shown that the anemia which develops in rats after irradiation by radiophosphorus

Table I

Hematocrit determinations on rabbits at selected times during determination of red blood cell survival time in days post injection

Rabbit	Day	0	8	14	26	35
1			39		32	36
2			42	42		
3		40	37	34	34	37
4				33	30	38
5	37	39	32			35

is more severe than can be accounted for by depression of hematopoiesis. Hemosiderin deposits in the reticuloendothelial system indicate rapid red blood cell breakdown. Kahn and Furth[5] using radioiron for determinations of red blood cell survival have shown that large doses of radiation (700 r to 1,000 r) cause increased red blood cell destruction in rabbits. Sheets *et al.*[9] using the Ashby method have shown that patients with carcinoma of the cervix may develop a random breakdown of erythrocytes seven to ten days after initiation of roentgen therapy.

The exact cause of accelerated disintegration of erythrocytes is unknown but various hypotheses may be considered.

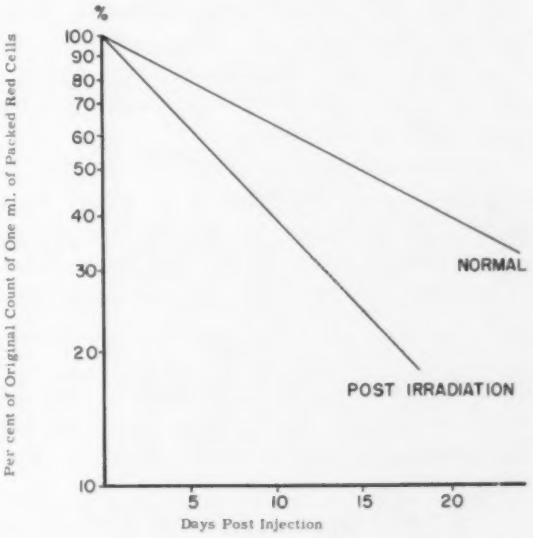

Fig. 2. Relative average erythrocyte half survival time (range 5 to 12 days) in 11 rabbits after 220 r (air) roentgen irradiation in ten divided doses

Kahn and Furth[5] feel that large doses of radiation damage capillary walls, allowing the escape of erythrocytes with consequent damage to the cells. After return to the circulation the damaged cells are prematurely removed. It seems probable that this process is unimportant with smaller doses of radiation. Repeated attempts to show damage to erythrocytes by *in vitro* irradiation have failed to demonstrate any discernible injury.[2,5,9] Such findings would also imply that the increased breakdown cannot be explained by direct damage to the intrinsic enzyme systems of the erythrocyte. Red blood cells showing increased disintegration in an irradiated host may show normal survival when transfused into a nonirradiated animal. On the other hand, red blood cells from a nonirradiated animal show accelerated breakdown when transfused into an animal previously irradiated.[5] Therefore, the mechanism by which irradiation promotes disintegration of erythrocytes appears to be systemic in mediation. Perhaps irradiation of an animal decreases the systemic production of some protective coating or essential constituent, such as an enzyme, necessary for sustaining normal longevity of the red blood cell. It is also conceivable that irradiation of an animal may lead to the production of toxic agents which injure the enzyme systems of erythrocytes or otherwise disrupt the integrity of red blood cells and thereby cause premature breakdown.

Further investigations of the effects of irradiation on erythrocyte survival with particular reference to the mechanism of and recovery from accelerated breakdown of red blood cells are under consideration.

SUMMARY

1. The average normal erythrocyte half survival time of 24 young adult rabbits by the sodium radiochromate method was fifteen days.

2. Erythrocyte half survival time for 11 rabbits after total body roentgen therapy of 220 r in air delivered in ten daily doses (about one-fourth the LD_{50} dose in thirty days) averaged 7.5 days or 47 per cent of the normal average.

3. Additional investigation is indicated to further establish the consistency of effect, quantitative relationship and mechanism by which irradiation reduces red blood cell survival.

Ronald E. Waggener, M.D.
University of Nebraska
College of Medicine
42nd and Dewey Avenue
Omaha 5, Nebraska

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NEUTRON ACTIVATION ANALYSIS OF BLOOD*

By RICHARD P. SPENCER, LT. MC USNR, THOMAS G. MITCHELL, LT. MSC USN, *and* E. RICHARD KING, CAPT. MC USN
BETHESDA, MARYLAND

CHEMICAL analysis of blood, though standardized in many aspects, is an involved and time consuming process. In addition, large sample quantities must be drawn if several anions or cations are to be investigated by macrotechniques. Further, samples subjected to standard analytic procedures are destroyed, and cannot be reassayed. This laboratory has therefore begun investigations on the use of neutron activation analysis, as a means of simultaneously, and nondestructively, determining the quantity of multiple constituents in samples of blood or other biologic materials.

PRINCIPLE

Neutron activation analysis depends upon the bombardment of a sample by a neutron beam, and measurement of the induced radioactivity. The technique was first suggested by Hevesy and Levi[13] in 1936, but its development awaited the availability of a suitable source of neutrons, such as the nuclear chain reactor. Clark and Overman[9] introduced the term "activation analysis" to replace the longer designation "radioactivation analysis."

Use of the procedure to provide data as to the chemical composition of materials is well known,[6] but little information is available on biologic applications. Tobias,[22] and independently Brues and Robertson,[7] were the first to study trace elements in biologic samples by means of activation techniques. Investigations of activation analysis in the life sciences have been concerned with either the detection of trace materials,[5,16,21,23] or estimation of the total radioactivity induced in a specimen.[10,18] To the best of our knowledge, this is the first reported systematic study of the applicability of neutron activation analysis to the routine determination of blood anions and cations.

CALCULATIONS

When tissue is exposed to a flux of thermal neutrons, interactions may occur between the bombarding particles and nuclei of atoms in the sample. One type interaction leading to a change of nuclear constituents is the neutron, gamma (n, γ) reaction, where the target nucleus absorbs a neutron and almost instantaneously (10^{-20} to 10^{-12} second) gives off a gamma ray. The resultant atom formed by this "radiative capture" may or may not be stable, depending on the final configuration. No transmutations occur in this process, and therefore an element may be determined by identification and quantification of the radioisotopes it produces (since each radioactive nuclide evolved has a self-characteristic mode of decay and half-life).

The (n, γ) events which occur depend upon the neutron flux, the concentration of the target material, and the neutron capture cross section.

$$N = n \cdot \sigma A \times 10^{-24} \cdot W \cdot f \cdot 6.023 \times 10^{23} / A_t \quad (1)$$

N is the number of events per second, n is the flux in neutrons/cm.^{2}/sec., W the weight of the target element (in grams), f is the fractional abundance of the particular isotope in the element, σA is the nuclear cross section in barn, A_t is the physical atomic weight of the target element, and 6.023×10^{23} is the number of atoms per gram molecular weight.

Events per second can be converted to

* From the Radioisotope Laboratory, United States Naval Hospital, and the Radioisotope School, United States Naval Medical School, National Naval Medical Center, Bethesda, Maryland. The opinions expressed herein are those of the authors, and do not necessarily reflect the views of the Medical Department, or the Naval Service at large.

microcuries by dividing by 3.7×10^4. Performing this step, and combining constants:

$$M=1.63\times10^{-5}\cdot n\cdot\sigma A\cdot W\cdot f/A_t \quad (2)$$

where M is the activity in microcuries, and σA is measured in barns (1 barn $=10^{-24}$ cm.^{2}).

The maximum activity of product nuclide results when the rate of production equals the rate of disintegration (this represents the "saturation" figure for the particular system). In the more general case, the material may not have been exposed to the neutron flux for a time sufficient to produce saturation. For such situations:

$$M=1.63\times10^{-5}\frac{\sigma A\cdot n\cdot W\cdot f}{A_t}(1-e^{-\lambda t_1}) \quad (3)$$

where λ represents the disintegration constant of the radionuclide produced, and t_1 is the length of time the sample has been exposed to the neutron flux. If analysis of the sample is delayed beyond the time the material has been removed from the neutron source, radioactive decay of the nuclide will occur:

$$M=1.63\times10^{-5}\frac{\sigma A\cdot n\cdot W\cdot f}{A_t}(1-e^{-\lambda t_1})(e^{-\lambda t_2}) \quad (4)$$

(the time interval following the cessation of neutron exposure is represented by t_2).

This general equation can be solved for W, the weight (in grams) of sample originally present:

$$W=\frac{M\cdot A_t}{1.63\times10^{-5}\cdot n\cdot\sigma A\cdot f\cdot(1-e^{-\lambda t_1})(e^{-\lambda t_2})} \quad (5)$$

The quantity of an anion or cation present in blood or other samples can then be determined by either of two methods:

1. By precise calculation (vide supra) if values for the neutron flux and time of exposure are available, and the sensitivity of the detection devices has been predetermined. This is essentially a problem of estimating the quantity of stable carrier, if the amount of radioactivity and its specific activity are known.

2. The induced radioactivity can be compared with that of a standard of known composition, subjected to the same neutron flux for exactly the same interval of time.

CHOICE OF NEUTRON FLUX

While reactors with a high neutron flux, used primarily for power production or physical experiments, have been employed for activation analysis,[17] they are usually not available for full scale biologic investigations. Hence, our calculations have been based on a flux of 2.5×10^8 neutrons/cm.^{2}/sec. This intensity is obtainable by the 5 watt model of a previously reported small reactor[3] suitable for medical or university laboratories. A flux of this magnitude can also be produced by large radium-beryllium sources,[12] and by use of a beryllium pot in conjunction with standard Van de Graaff high voltage generators[8,12] available in several medical centers and physics laboratories (these latter sources, however, can maintain the flux only over a small sample area). The threshold energy for neutrons from beryllium is 1.63 mev.,[4] and sources of gamma rays whose energy equals or exceeds this value may potentially be used with Be as a neutron source (these particles, however, must be thermalized). Thus the choice of 2.5×10^8 neutrons/cm.^{2}/sec. represents a flux which can be achieved by a number of procedures available to smaller laboratories.

RADIOACTIVITY INDUCED IN BLOOD

Blood contains a number of anions and cations which are fractionated between cellular components (particularly red blood cells) and plasma. Based on the average concentration of each of the principal elements in adult human blood, and using a value of 2.5×10^8 neutrons/cm.^{2}/sec. as the flux, the radioactivity induced in 10 ml. aliquots of blood was calculated (Table 1). The situation is simplified, because for the short irradiation periods under consideration, no significant radioactivity is induced in carbon, hydrogen, oxygen, or nitrogen. Values in Table 1 were calculated for

TABLE I

RADIOACTIVITY INDUCED IN 10 ML. BLOOD BY A FLUX OF 2.5×10^{8} NEUTRONS/CM.^{2}/SEC.

End Product Isotope	Concentration of Chemical Element in 10 ml.*	Activity in μc following Irradiation of 10 ml. Sample for Indicated Time			1,000 dpm per 10 ml. at Indicated Time of Irradiation		
		1 hr.	5 hr.	Saturation†	1 hr.	5 hr.	Saturation†
Na^{24}	33 mg. s	0.14	0.65	3.1	320.0	1,430	6,900
Na^{24}	2.5 mg. r	1.07×10^{-2}	4.9×10^{-2}	0.23	23.8	109	510
Mg^{27}	0.1 mg. s	5.55×10^{-5}	Z	Z	0.123	Z	Z
Mg^{27}	0.66 mg. r	3.66×10^{-4}	Z	Z	0.810	Z	Z
P^{32} ii	0.3 mg. p	1.56×10^{-5}	7.8×10^{-5}	7.8×10^{-3}	0.035	0.173	17
S^{35} ii	0.1 mg. s	4.1×10^{-8}	2.3×10^{-7}	1.38×10^{-6}	9.0×10^{-6}	5.0×10^{-4}	0.3
S^{37} ii	0.1 mg. s	3.0×10^{-7}	Z	Z	6.7×10^{-4}	Z	Z
Cl^{38}	27 mg. w	0.29	0.42	0.42	645.0	935.0	935.0
Cl^{38}	34 mg. p	0.36	0.53	0.53	800.0	1,180.0	1,180.0
K^{42} nn	1.6 mg. s	8.6×10^{-4}	3.1×10^{-3}	1.57×10^{-2}	1.91	8.58	34.9
K^{42} nn	42 mg. r	1.6×10^{-2}	7.0×10^{-2}	0.29	35.5	158.0	645.0
Ca^{45}	1 mg. s	2.54×10^{-7}	1.14×10^{-6}	1.27×10^{-3}	5.6×10^{-4}	2.5×10^{-3}	28.2
Ca^{47}	1 mg. s	5.8×10^{-9}	2.9×10^{-8}	9.7×10^{-7}	1.3×10^{-5}	6.5×10^{-5}	2.1×10^{-3}
Ca^{49}	1 mg. s	2.0×10^{-4}	Z	Z	0.444	Z	Z
Fe^{59}	5.2 mg. w	6.7×10^{-7}	3.5×10^{-6}	1.1×10^{-3}	1.5×10^{-3}	7.8×10^{-3}	2.44
Fe^{59}	10^{-2} mg. s	1.3×10^{-9}	6.7×10^{-9}	2.2×10^{-6}	2.9×10^{-6}	1.5×10^{-5}	4.8×10^{-3}
Cu^{64}	10^{-2} mg. s	1.0×10^{-4}	4.57×10^{-4}	1.93×10^{-3}	0.222	1.02	4.30
Cu^{66}	10^{-2} mg. s	4.3×10^{-4}	Z	Z	0.950	Z	Z
Br^{80m}	0.1 mg. s	1.04×10^{-3}	4.0×10^{-3}	7.6×10^{-3}	2.35	8.92	16.8
Br^{80}	0.1 mg. s	1.96×10^{-2}	2.18×10^{-2}	2.18×10^{-2}	43.5	48.5	48.5
Br^{82}	0.1 mg. s	1.3×10^{-4}	6.3×10^{-4}	6.5×10^{-3}	0.29	1.40	14.4
I^{128} bb	10^{-3} mg. s	6.48×10^{-4}	8.0×10^{-4}	8.0×10^{-4}	1.44	1.78	1.78
Zn^{69}	10^{-2} mg. p	6.0×10^{-5}	1.1×10^{-4}	1.1×10^{-4}	0.134	0.241	0.246
Assumed concentrations:							
Co^{60m}	10^{-5} mg. p	1.23×10^{-5}	1.25×10^{-5}	1.25×10^{-5}	0.027	0.028	0.028
Rb^{86m}	10^{-5} mg. p	1.73×10^{-8}	Z	Z	3.8×10^{-5}	Z	Z
Mn^{56}	10^{-5} mg. p	2.31×10^{-6}	7.11×10^{-6}	9.08×10^{-6}	5.1×10^{-3}	1.6×10^{-2}	2.0×10^{-2}
Al^{28}	10^{-5} mg. p	3.37×10^{-7}	Z	Z	7.3×10^{-4}	Z	Z
Si^{31}	10^{-5} mg. p	1.1×10^{-9}	3.19×10^{-9}	4.04×10^{-9}	2.2×10^{-6}	7.1×10^{-6}	9.0×10^{-6}
$Cd^{107,111,115m,115}$	10^{-5} mg. p	Less than 3 dpm at 10 hours.					

* s is serum, r red blood cells, p plasma, w whole blood.
Amount of element × fractional abundance gives quantity of precursor.
Z = unchanged from value at one hour.
ii = non-protein form; higher value if S or P present in proteins in sample.
nn = not including activity due to naturally occurring K^{40}.
bb = both protein-bound and non-protein iodine.
† Value at 10 hours or true saturation, whichever time interval is shorter.

exposure intervals of 1 hour, 5 hours, and "saturation" (10 hours or true saturation, whichever time period was shorter). The advantage of using such short periods is that results are rapidly available, where with other reports on the use of activation analysis in trace metal determination, up to one month was required for irradiation.[16,19]

Of the various nuclides produced, thirteen are theoretically present to the extent of 30 disintegrations per minute (dpm) or greater, after a one hour irradiation. These are Na^{24}, Cl^{38}, K^{42}, Ca^{49}, Cu^{64}, Cu^{66}, Br^{80}, Br^{80m}, Br^{82}, I^{128}, Zn^{69}, Mg^{27}, and P^{32} (m refers to the first metastable form of an isomeric pair. If these nuclides were to be quantitatively distinguished from each other, it would be possible to estimate six cations (Na, Mg, K, Cu, Zn, Ca) and four anions (Cl, Br, I, P) in blood plasma. In addition to these isotopes, nuclides of

TABLE II

DISINTEGRATION OF RADIONUCLIDES INDUCED IN PLASMA OR SERUM TO THE EXTENT OF 30 DPM OR GREATER BY ONE HOUR EXPOSURE TO A BEAM OF 2.5×10^8 NEUTRONS/CM.^{2}/SEC.

$T=0$ refers to the disintegrations per minute of the sample at the time of removal from the neutron flux

Isotope	dpm at $T=0$	Gamma Factor[1]	Gamma Counts/Min.	Beta Factor[2]	Beta Counts/Min.
Na^{24}	320,000	2.00	640,000	1.0	320,000
Cl^{38}	800,000	0.47	376,000	1.0	800,000
Br^{80m}	2,350	2.00	4,700	0	0
Br^{80}	43,500	0.21[3]	9,135	0.91 0.03 positrons	39,585
Br^{82}	290	xx	xx	1.00	290
I^{128}	1,440	0.07	101	0.95	1,368
K^{42}	1,909	0.20	381	1.0	1,909
Ca^{49}	444	1.00	444	xx	xx
Cu^{64}	222	0.38[4]	84	0.91 0.19 positrons	202
Cu^{66}	950	0.07	66	1.00	950
Zn^{69}	134	0	0	1.00	134
Mg^{27}	123	1.2	148	1.00	123
P^{32}	35	0	0	1.00	35

[1] Average number of gamma rays per disintegration.
[2] Average number of beta rays per disintegration.
[3] Primary gamma rays contribute 0.15; additional 0.06 from annihilation of positrons.
[4] Gamma rays entirely from positron annihilation.
xx= Reliable figures not available as of September, 1956.

cobalt (Co^{60m}) and manganese (Mn^{56}) may be near the limit of detection, depending upon the initial concentration of their precursors in the blood stream. The value of 30 dpm was chosen as the critical limit, as it represents twice the "background" of the instrument used.

DISTINGUISHING THE INDUCED RADIONUCLIDES

Not all of the isotopes mentioned above emit both beta and gamma rays. In Table II are listed the isotopes, and the average number of detectable beta and/or gamma rays per disintegration. It can be seen that efficiency of detection will vary, being high for sodium and chlorine and low for iodine.

Not only is the efficiency of detection important, but the half-life of the nuclide also figures in whether the isotope can be quantitatively determined in a sample. For example, the half-life of Cu^{66} (0.085 hour) is so short that its radioactivity is rapidly dissipated. The nuclides induced in blood to the extent of 30 dpm or greater after a one hour exposure to the neutron beam are listed in Table III, along with figures indicating the total number of disintegrations at the time of removal of the sample from the reactor, and twelve hours later. It will be seen that twelve hours after irradiation, only six isotopes (Na^{24}, K^{42}, Cu^{64}, Br^{80m}, Zn^{69}, and P^{32}) remain to the extent of 30 dpm or greater. As will become apparent, the emissions from these isotopes are completely dominated by the Na^{24} and Cl^{38} spectrum.

GAMMA RAY SPECTRAL CURVES

To distinguish between the radioisotopes in plasma, the techniques of beta ray spectroscopy or gamma ray spectroscopy have applications.[20] Both techniques are under investigation. However, because of its wider applicability, gamma ray spectroscopy appears to have more to offer in this case, and results are reported here.

As can be seen in Table III, all of the

TABLE III

ISOTOPES PRODUCED TO THE EXTENT OF 30 DPM OR GREATER BY ONE HOUR BOMBARDMENT OF HUMAN PLASMA OR SERUM (10 ML.) BY 2.5×10^8 NEUTRONS/CM.^{2}/SEC.

$T=0$ refers to time of removal of sample from neutron source. $T=12$ represents twelve hours later; b is beta, g is gamma, p is positron

Isotope	Half-Life in Hours	Type of Emission	dpm at $T=0$	dpm at $T=12$	Ratio at 12 hr. ($Na^{24}=100$)
Na^{24}	15.0	b g	320,000	184,640	100.0
Cl^{38}	0.622	b g	800,000	2	0.001
Br^{80m}	4.6	g	2,350	388	0.21
Br^{80}	0.3	b g p	43,500	0	0
Br^{82}	35.9	b g	290	215	0.12
I^{128}	0.417	b g	1,440	0	0
K^{42}	12.5	b g	1,909	983	0.53
Ca^{49}	0.142	b g	444	0	0
Cu^{64}	12.8	b g p	222	116	0.06
Cu^{66}	0.085	b g	950	0	0
Zn^{69}	0.867	b	134	0	0
Mg^{27}	0.158	b g	123	0	0
P^{32}	348.0	b	35	35	0.02

detectable radionuclides induced in blood, with the exception of Zn^{69} and P^{32}, produce one or more gamma rays per disintegration. The major gamma emissions of these nuclides are presented in spectral fashion in Figure 1. It should be borne in mind that many of the following comments are applicable to beta ray spectroscopy, since each of the isotopes (with the exception of Br^{80m}) produces one or more beta rays per disintegration (Fig. 2).

Gamma ray spectra were recorded by means of the apparatus diagrammed in Figure 3. The baseline voltage of the pulse height analyzer (Nuclear Model 1810) was varied at a constant rate by a motor driven potentiometer. Pulses within 1.5 volts above the baseline were fed through a scaler and count rate meter to a linear recording galvanometer (Houston Recti-Riter). The potentiometer was driven at a rate of one turn per 50 minutes, and the recording sheet of the galvanometer moved 12 inches per hour (10 inches in fifty minutes). Commercial continuous scanning spectrometer systems are also available.[1]

Spectra were determined for separate samples of Na^{24}, K^{42} and Cu^{64}, using amounts comparable to those found in human plasma after neutron irradiation of one hour. The three isotopes are theoretically present to the extent of 1,410:8.6:1.0, while the ratio used in the experiment was 1,000:10:1. The three radionuclides were then mixed together and another gamma ray spectrum obtained (Fig. 4). The resultant curve was identical with that of pure Na^{24}; the photoelectric peaks of K^{42} and Cu^{64} were masked by the large number of Na^{24} radiations. Because of its presence in large quantity, and the similarity of many of its radiations to radiosodium, Cl^{38} would also interfere with the determination of radiopotassium and radiocopper. Hence determining of Cu^{64} and K^{42} radiations is practicable only after their separation from Na^{24} and Cl^{38}.

Because of their abundance, and the emissions from their radioisotopes, sodium and chlorine can be detected and estimated directly on plasma samples, without the removal of other substances. Due to the short half-life of Cl^{38} (0.622 hour), the isotope has been dissipated 12 hours after irradiation has been completed. Radiosodium at this time, however, is present to the extent of (184,640 dpm/320,000 dpm) or 58 per cent of its original activity. The intense radiation from neutron activated sodium in blood has been noted previously.[17]

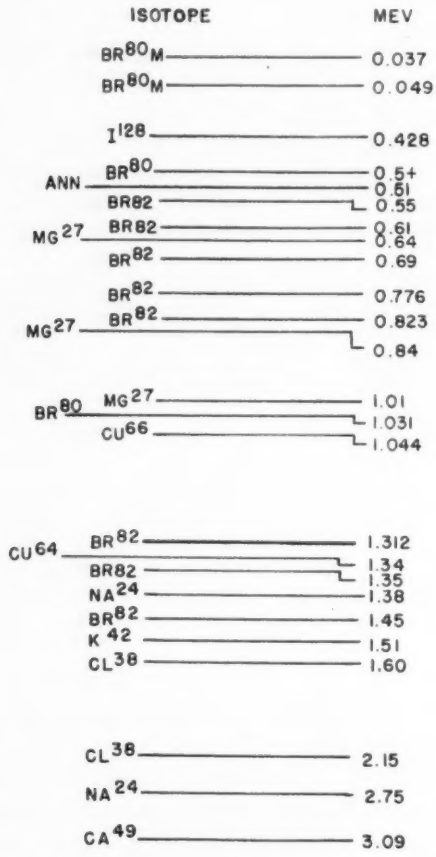

FIG. 1. Spectrum of major gamma emissions from isotopes listed in Table II. M = first state of isomeric pair. ANN = 51 mev. from annihilation reaction of positrons from Cu^{64} and Br^{80}.

Sodium analysis may be performed many hours after irradiation, at which time other induced isotopes have disappeared.

TECHNIQUE OF IRRADIATION

There are several points, although minor in nature, which had to be considered prior to irradiation, since they affect the over-all efficiency of activation analysis.

1. Type of Container. The sample holder should not be affected by the heat of the reactor, and must not possess a high capture cross section for thermal neutrons. Polyethylene, graphite, and quartz may be employed to advantage, although the latter often contains traces of boron. We have used polyethylene tubes, 15 by 35 mm. outer dimensions. Minimal, short lived radioactivity is induced in the container (probably chlorine), and this has presented no problem.

2. Decontamination of Container. It is essential that the sample holder be free of contaminants, and hence a washing must be carried out. For this purpose, materials which contain sodium (such as soaps and most detergents), or chlorine, should be scrupulously avoided. Tubes were washed in nitric acid, distilled water, and then air dried. In all stages of the work, care was exercised to avoid contact with materials which have a high thermal neutron capture cross section.

3. Type of Sample. Fresh drawn plasma is readily adaptable to analysis, when a flux of 2.5×10^8 neutrons/cm.^{2}/sec. is employed. Reactors generating very high neu-

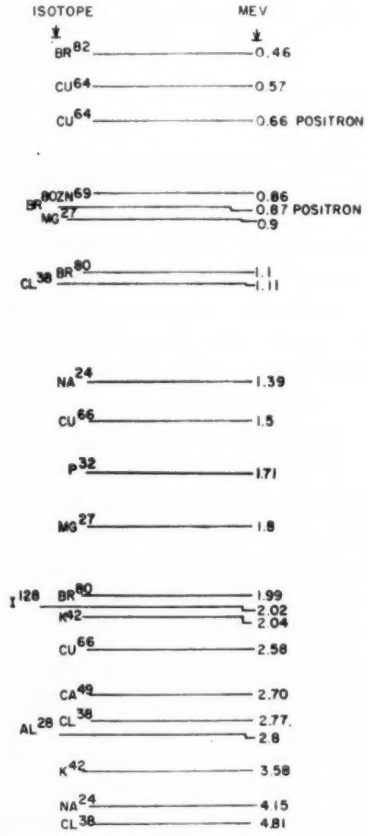

FIG. 2. Spectrum of major beta emissions from isotopes listed in Table II.

tron fluxes tend to heat samples placed directly into the glory hole (but not necessarily specimens in access ports). There is thus the danger that water in plasma will boil, expand, and fracture the container. If high flux reactors are employed, dried samples of plasma may be utilized, without danger of a boiling liquid. We use commercially available dried human serum of known composition as a standard (Versatol by Warner-Chilcott Laboratories, or Clinical Chemistry Control Serum by Hyland Laboratories).

4. Preparation of Plasma. Ordinary anticoagulants are not suitable when plasma is to be subjected to activation analysis. Heparin contains sodium, and the standard oxalate anticoagulant is usually supplied as the potassium salt. To avoid the addition to extraneous sodium or potassium to the sample, ammonium oxalate or citric acid may be employed. Siliconized or paraffined tubes are useful in preventing blood from clotting for a long enough period to allow plasma to be separated from cellular elements by centrifugation. A recently described differential closed centrifuge[24] may be of value in this separation.

5. Counting Tube. Once neutron bombardment has been accomplished, the tube and sample can be taken from the irradiation source and placed directly in a scintillation detector for counting. This has the disadvantage of recording radioactivity which may have been induced by contaminants in the container walls. Breaking open the container and transferring its sample to a "cool" tube, may entail a loss of material and the escape of substances

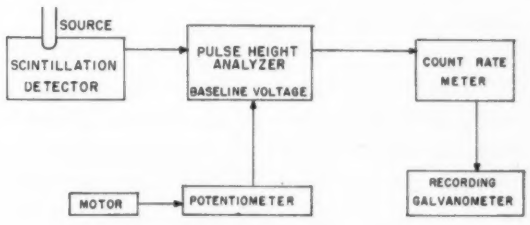

Fig. 3. Diagram of gamma ray spectrographic apparatus.

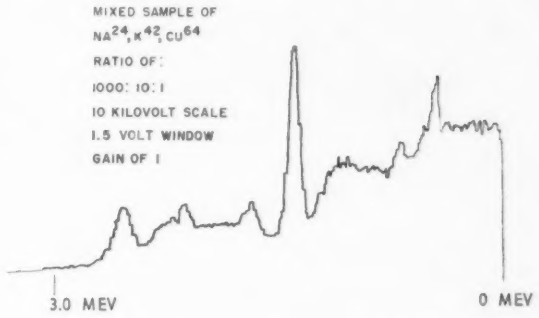

Fig. 4. Gamma ray spectrum of artificially admixed isotope sample.

which have volatilized. If the tube is to be broken open, it should preferably be accomplished in a cold environment, within a hood or dry box. We have employed counting directly from the irradiated tube, and after sample transfer results have been identical.

RESULTS OF IRRADIATION

Serum samples have been subjected to flux densities from 10^7 to 10^9 neutrons/cm.^{2}/sec., in a pool-type nuclear reactor. In Figure 5 is shown the gamma ray spectrum from 10 ml. dried serum, run one hour after exposure of the sample to 3×10^8 neutrons/cm.^{2}/sec. for 20 minutes. It can be seen that the curve approximates that of the sodium tracing.

Decay of the samples has been followed by beta and gamma counting. Twelve hours after irradiation, Na^{24} is the only gamma emitter present to a significant degree, and sodium analysis may be run on the sample by comparing it with a standard handled in identical fashion.

DISCUSSION

Utilizing this low flux for a one hour irradiation, separating the isotopes in thirty minutes, and then counting in thirty minutes, it should be possible to analyze blood for 10 or more components in two hours. Further, the analysis is nondestructive, and the sample will still be available for repeated assays.

The essential problem is to separate the

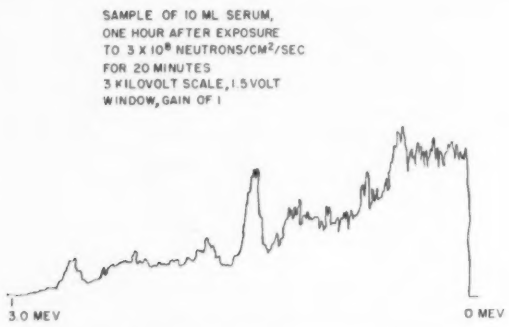

FIG. 5. Gamma ray spectrum of neutron irradiated serum.

radionuclides from each other. Particularly Na^{24}, with its strong emissions, must be removed from other isotopes. Two approaches are possible:

1. Separation of elements prior to bombardment. Anions or cations necessary to accomplish this separation must be so chosen that they will not become radioactive themselves during irradiation. Hence, the ammonium radical, nitrates, oxalates, cyanates, and various organic radicals may be employed, as well as mixtures of trace materials which possess a small thermal neutron capture cross section. Separation prior to neutron exposure must then primarily depend upon physical means, such as differential solubilities, electrochromatography,[11] or ion exchange methods.[2]

2. Separation of elements following neutron bombardment. Any chemical desired may be added after irradiation has been accomplished, as long as it is not radioactive itself (this may rule out uranyl salts). The sole requirement is that partial or complete separation be accomplished rapidly, so that radioactive decay does not become significant. Passage through an exchange column may be of value.[16] We have been trying "group-precipitating" reagents, with a fair degree of success. Silver nitrate is used to precipitate the halogens relatively free of other materials. The precipitate can then be further separated by chemical means, and by the application of gamma ray spectroscopy.

Short exposure of other biologic tissues to a low neutron flux may be exceedingly useful in quantitative analysis. Since tissues contain significantly less sodium and chlorine than serum (and proportionally more protein, sulfur, and phosphorus), activation analysis may be directly applied to the estimation of constituents in tissue samples[19] and red blood cells (although in the former, interstitial water and electrolytes would be present). Our preliminary work on erythrocyte analysis has shown that neutron activation is applicable. For example, in erythrocytes, the following relationship exists following neutron bombardment.

Isotope	Estimated Normal Concentration Stable Element in Red Blood Cells	dpm after One Hour in Neutron Flux
Na^{24}	2.5 mg./10 ml.	23.8×10^3
Mg^{27}	0.66 mg./10 ml.	0.8×10^3
K^{42}	42.0 mg./10 ml.	35.5×10^3

Tissues which contain trace elements present no problem at the low flux employed. Certain trace materials have a high neutron capture cross section[15] and may be estimated by slightly higher flux densities.

CONCLUSIONS

1. The application of neutron activation analysis to quantitation of anions and cations in blood is discussed, utilizing a flux of 2.5×10^8 neutrons/cm.^{2}/sec. This flux can be obtained by the use of radium-beryllium sources, Van de Graaff-beryllium systems, and nuclear reactors. The time of irradiation is only one hour, and the technique is nondestructive to the specimen.

2. Thirteen isotopes are theoretically produced to the extent of 30 dpm or greater following the exposure of 10 ml. plasma to this flux for one hour. These isotopes represent six cations (sodium, magnesium, potassium, copper, zinc, calcium) and four anions (chlorine, iodine, bromine, phos-

phorus). Hence, if complete delineation were possible, ten electrolytes in blood could be estimated by neutron activation analysis at this low flux. In addition, isotopes of cobalt and manganese may be at the limit of detection.

3. Each of the isotopes produced to the extent of 30 dpm or greater, with the exception of P^{32} and Zn^{69}, gives off gamma rays during its disintegration. All of the radionuclides produced to this extent, except Br^{80m}, emit beta rays. The applicability of gamma ray and beta ray spectroscopy, in distinguishing between these isotopes, is discussed. In addition, differences in half-life may enable certain of the isotopes to be detected after more short-lived components have been dissipated.

4. Emissions from Na^{24} and Cl^{38} tend to dominate the gamma ray spectrum of neutron irradiated blood. Hence, sodium and chlorine may be estimated directly by activation analysis. Techniques of separating other radioisotopes present in the sample, to eliminate sodium and chlorine, are discussed.

5. Neutron activation analysis may be directly applicable to the determination of red blood cell composition, since these cells have a low content of sodium and chlorine, and can be obtained relatively free from plasma. Applications to tissue analysis are also pointed out.

Lt. R. P. Spencer, MC, USNR
Radioisotope Laboratory
U. S. Naval Hospital
Bethesda 14, Maryland

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MALIGNANT MELANOMA*

A COMBINED SURGICAL AND RADIOTHERAPEUTIC APPROACH

By ROBERT J. DICKSON, M.D.† (Cantab.), D.M.R.T.
BALTIMORE, MARYLAND

IN MOST classifications of the radiosensitivity of tumors, malignant melanoma is grouped with the sarcomas of bone and soft tissue as a radioresistant lesion. It is, however, seldom stated whether this opinion is based on personal experience or whether the statement has simply been copied from one publication to another. Similarly, it is often said that radiation therapy, except when used in cauterizing doses, is useless in the treatment of this disease,[11,12] although in centers where well planned radiation therapy is employed, there is evidence that this method is of definite value.[4,8] As Cade[4] states, "it is unfortunate that radio-resistance should have been given a meaning synonymous with that of unsuitability for radiation." It is probably true that no malignant melanotic tumor is curable by radiation alone, and that surgical excision of involved areas offers the patient the best chance of survival, but local recurrence in the primary site or in the lymph node areas is all too frequent. For this reason a very wide, and frequently mutilating, operative procedure is attempted. An alternative to this drastic surgery is suggested in this paper.

Neither surgery nor radiation therapy alone will cure a majority of patients with malignant melanoma, and it is of some interest to inquire whether a combination of these modalities will improve the prognosis. The object of this study therefore was to attempt to evaluate the efficacy of postoperative irradiation, as advocated by the late Dr. G. E. Richards, Director, Ontario Institute of Radiotherapy at Toronto General Hospital. To this end, all case histories in the tumor registry of that hospital were drawn and examined so that cases which had not been treated in this fashion were available for comparison of end-results. Furthermore, the records of the radiotherapy department of Johns Hopkins Hospital and of the tumor registry of the Public Health Service Hospital in Baltimore were examined.

No case of prepubertal melanoma was included in the series, for it is well known that such lesions are indistinguishable histologically from malignant melanoma, although the clinical course may be entirely benign. Secondly, melanoma of the uveal tract was excluded, for this condition appears to run a more chronic course than melanoma of the skin. All available sections were re-examined by an independent pathologist who was unaware of the clinical story or of the ultimate outcome of the case, and a few cases were discarded on his doubt as to the malignancy of the original lesion. In some instances the original sections could not be obtained and these cases were excluded if the subsequent course of the case was entirely benign. If, however, the history showed that metastatic disease developed later, the case was included in the study. The total number of case histories finally available was 254, consisting of 188 from the Toronto General Hospital and 66 from the two hospitals in Baltimore.

AGE AND SEX

Table 1 shows the age and sex incidence in selected series of malignant melanoma from the literature, compared with the present study. It will be seen from this table that, in common with other reports, there is little difference in the sex distribution in this disease and that it occurs most commonly in the older age groups, with a peak in the fifty-one to sixty year range. The youngest patient in the present series

* Based on a paper read at the Eighth International Congress of Radiology, July, 1956, Mexico City, Mexico.
† Radiologist-in-charge-of-Radiotherapy, Johns Hopkins Hospital.

TABLE I

PERCENTAGE AGE AND SEX INCIDENCE

Author	No. of Cases	Sex Per Cent		Age Per Cent							
		M	F	0–10 yr.	11–20 yr.	21–30 yr.	31–40 yr.	41–50 yr.	51–60 yr.	61–70 yr.	71– yr.
Ackerman[1] 1948	75	59	41	1.2	4.0	7.5	12.0	17.3	24.0	26.7	33.3
Affleck[3] 1936	266	57	43	—	1.8	15.5	20.0	15.5	22.2	14.2	10.2
Daland and Holmes[6] 1939	174	44	56	0.6	2.3	8.0	8.5	19.5	18.4	26.4	16.0
de Cholnoky[7] 1941	117	—	—	1.7	6.8	16.2	17.0	19.6	24.8	11.1	2.5
Hall *et al.*[9] 1952	222	53	47	0.6	3.1	10.1	17.5	22.1	13.9	22.1	7.5
Pack *et al.*[12] 1947	718	50	50	1.4	20.1	20.1		34.8		23.4	
Scharnagel[15] 1933	81	36	64	3.8		10.1	6.3	12.7	17.7	30.4	19.0
Sylvén[16] 1949	341	43	57	3.2	2.9	13.5		37.0		43.0	
Webster *et al.*[19] 1944	162	57	43	6.8	3.4	10.3	19.8	18.5	14.4	17.8	8.9
Wright[20] 1949	109	45	55	1.0	1.0	8.2	11.0	21.8	15.5	21.8	19.3
Dickson, Present Series	254	56	44	—	3.1	11.0	12.6	16.5	24.0	19.6	11.8

was a boy of twelve. There is no notation in the chart as to the occurrence of puberty in this child, but he died of widespread melanomatous deposits a few months after his original lesion was excised and he is therefore included in the series. The oldest patient was eighty-nine years of age.

BODY DISTRIBUTION

Table II shows an analysis of the distribution of the lesions in this group as compared with other large series of cases, and again it will be noted that there is a general similarity in all reports. This similarity would be still more noticeable if lesions of the eye were excluded as they were in this present group. The areas most commonly involved are the head and neck and the lower limb, with the trunk and upper limb being somewhat less frequently affected. Note can be made of the percentage of cases, albeit small, of malignant melanoma of the external female genitalia, a lesion stated by Way[18] to be excessively rare.

Combining the age at first treatment with the distribution of lesions in the body reveals that, in this series at least, malignancy tends to occur at a later age in the

TABLE II

PERCENTAGE DISTRIBUTION OF LESIONS

Author	Lower Limb	Upper Limb	Head and Neck	Trunk	Female Genitalia	Brain	Unknown	Eye
Ackerman[1] 1948	35.0	9.0	32.0	24.0	—	—	—	—
Adair[2] 1936	24.7	12.5	21.3	21.0	3.0	—	2.0	10.9
Affleck[3] 1936	25.0	23.3	24.1	22.2	0.8	—	—	4.5
Daland and Holmes[6] 1939	31.6	6.4	25.2	17.8	0.6	1.7	2.3	14.4
de Cholnoky[7] 1941	26.0	15.0	40.0	—	—	—	—	—
Hall *et al.*[9] 1952	21.9	16.2	30.6	23.1	0.6	—	7.5	—
Pack *et al.*[12] 1947	27.0	13.7	25.2	19.8	3.6	—	1.5	8.6
Preston *et al.*[14] 1954	22.2	8.9	14.7	27.1	—	—	7.6	18.2
Scharnagel[15] 1933	32.2	6.1	28.5	24.7	6.2	—	2.4	—
Sylvén[16] 1949	31.0	8.4	33.6	26.6	—	—	0.3	—
Webster *et al.*[19] 1944	31.4	14.8	27.1	17.2	—	—	10.4	—
Wright[20] 1949	27.0	13.0	26.0	28.0	3.0	—	2.0	—
Dickson, Present Series	30.0	13.8	31.5	17.7	3.9	0.8	2.0	—

head and neck than in other areas (Table III). Table IV shows the sex and the distribution of lesions about the body. Whereas the limbs are apparently involved with equal frequency in the sexes, lesions of the head and neck and of the trunk are more common in males, but it is doubtful if this finding is significant. It was not possible to determine accurately the frequency of pre-existing melanomata, but in the small number of cases in which this was noted in the chart, approximately two-thirds gave a history of a pre-existing lesion. Also, the role of trauma in the production of malignancy could not be estimated, but there did not appear to be any increased tendency to malignant change in lesions exposed to recurring trauma—neck, belt-line, heel and sole of the foot—as compared with other areas. Trauma was mentioned as a factor in only about 10 per cent of cases but this is almost certainly an underestimate. Only 2 patients in the series are known to have become pregnant, but in 1 the disease was in abeyance at the time and no evidence of activation of her condition occurred (Case 11). In the other, four months after excision of positive axillary lymph nodes she became pregnant. Following delivery she noted a cough. Chest roentgenograms showed pulmonary metastases and she died two months later.

STAGING OF CASES

The classification suggested by Sylvén[16] was adopted. The status of the patient at his first appearance at hospital for definitive therapy was determined from the available clinical and laboratory information and the case placed in the appropriate stage of the following classification: Stage I. Localized melanoma confined to the skin. Local recurrences and near-by deposits in cutaneous lymphatics are included. Stage II. Cases with regional lymph node metastases confined to one gland station only. Stage III. Metastatic involvement of two or more groups of lymph nodes, and cases with distant metastases evidencing generalized tumor process.

In this series, the relative frequency was: Stage I, 102 = 43.5 per cent; Stage II, 93 = 39.3 per cent; Stage III, 39 = 16.7 per cent.

TREATMENT

The treatment policy at Toronto General Hospital was to operate on all cases of malignant melanoma in Stages I, II and occasionally III with a wide excision of the primary tumor and the immediate lymph drainage areas, and then to give postoperative radiation therapy to all areas which were found on histologic examination to contain disease. Not infrequently, however, this policy was not adopted and a number of cases treated by surgery alone was found. In the cases from the two Baltimore hospitals, a few were treated by surgery with irradiation, but the majority received no radiation therapy in the initial stages, being referred only for palliative irradiation when the disease had recurred. The majority of Stage III lesions were treated by palliative means only.

RADIATION THERAPY

Radium and roentgen rays were used with almost equal frequency. Surface radium molds or interstitial radium implants were employed in the treatment of the primary area but the dosage used could not be calculated as it was often expressed in milligram-hours and all the factors concerned are not available. Teleradium therapy both to the primary and to metastatic sites was given to several patients, the dosage varying between 4,800 r and 6,500 r in four to six weeks. Those receiving roentgen therapy were usually given 100 kv. radiation to a dose of 5,000 r in ten days to the primary area with an estimated tumor dose of 4,000 r to 5,000 r to lymph node-bearing areas at either 200 or 400 kv. in about five weeks. Other patients were treated by high-voltage radiation to the primary area as well as to the lymph nodes particularly if the primary lesion was extensive or if it had infiltrated deeply. The number of cases treated by each method

TABLE III

AGE AND BODY DISTRIBUTION

Age (years)	Lower Limb	Upper Limb	Head and Neck	Trunk	Vulva	Brain	Unknown	Total
11–20	4	1	1	2				8
21–30	10	3	9	6				28
31–40	13	4	8	4		1	2	32
41–50	14	6	9	12	1			42
51–60	16	10	17	12	4		2	61
61–70	11	4	24	8	3			50
71–80	4	4	10		1	1	1	21
81	3	2	2	1	1			9
Unknown	1	1	1					3
Total Cases	76	35	81	45	10	2	5	254

was insufficient to identify any marked superiority for any particular method, long term survivors occurring in each group. It may be worth mentioning that, in contradistinction to the opinion sometimes expressed,[13] implantation of radium to the excisional scar of a primary malignant melanoma did not lead to dissemination of disease. Many cases so treated survived for long periods without either local recurrence or metastatic deposits. On the other hand, there would not appear to be any particular advantage for this method of treatment and it may be considered to have little value in this disease.

SURGERY

Although wide excisional surgery was adopted as the policy of primary treatment, a considerable number of cases even of Stages I and II had only a local excision or electrocautery of the lesion. Sometimes this was followed by wider excision but not infrequently radiation therapy was delivered immediately following the local treatment and no further surgery was attempted. Local, inadequate treatment given previously is considered separately in the statistical analysis of results, although it is not the purpose of this paper to explore the relative merits of different surgical approaches to the problem.

TABLE IV

SEX AND BODY DISTRIBUTION

Site	Male	Female	Total	Per Cent
Lower Limb	38	38	76	30.0
Upper Limb	19	16	35	13.8
Head and Neck	51	30	81	31.5
Trunk	31	14	45	17.7
Female Genitalia	—	10	10	3.9
Brain	1	1	2	0.8
Unknown	3	2	5	2.0

RESULTS

A total of 234 cases was available for statistical analysis, all having been followed to death, for at least five years if still alive, or until lost to further follow-up examination. No patient treated more than five years ago was excluded from the analysis whose sections met with the histologic criteria of malignancy or who subsequently developed metastatic melanomatous disease, and all patients who were lost to follow-up or whose death was certified as due to intercurrent disease were included. The cases were placed in one of three categories, depending on the treatment when first diagnosed as suffering from malignant melanoma. First, those patients who had received "meddlesome and incompetent treatment,"[17] either by local surgery, desiccation, application of caustics or the traditional tying of a string around the lesion, were considered as being given only "local treatment." If, however, defini-

TABLE V

STATUS OF PATIENTS FIVE YEARS AFTER TREATMENT

Type of Treatment	Alive without Disease	Alive with Disease	Dead with Disease	Dead without Disease	Total
Wide Surgery	6	5	29	2	42
Local Treatment	6	8	57		71
Radiation Therapy	44	6	61	10	121
Total Cases	56	19	147	12	234

tive therapy, either surgical or by irradiation was given *less than one month* following the inadequate treatment, the case was considered in the appropriate one of the other two groups. The second group therefore included all patients whose sole therapy was radical surgery, either as an initial treatment or subsequent to local interference. Every patient who received any form of radiation therapy was included in the third category whether the previous treatment had been a biopsy, a local excision, or radical surgery. Table v shows the relative sizes of these groups together with the status of the patients five years after treatment. Seventy-one cases were treated initially by the application of caustic solutions or by local surgical removal without any further treatment within a one month period, 42 by definitive radical surgery, and the remaining 121 cases received radiation therapy either by radium or by roentgen rays immediately subsequent to the initial surgical intervention. It should be stressed that in many of the cases the surgery was local and that many Stage III cases are included in the group receiving radiation therapy. The cases listed as alive without disease were assessed at the end of the five year period but several of them are still alive twenty years and more after their initial treatment. In the column "alive with disease" are included those patients who survived more than five years but who died at a later date with obvious evidence of metastasis. Those who died of their disease within the five year period form the largest group, 147 in all, and a few cases, 12 in number, died before that period had elapsed and at autopsy showed no evidence of malignancy. For evaluation, however, they are considered as having died of their disease.

The statistical analysis of results is given in Table VI. From this it will be seen that of the 121 cases in which radiation therapy was used, 41 per cent survived the conventional five year period. Approximately one-quarter of the patients treated by excisional surgery without irradiation survived the corresponding period, and those whose treatment consisted of local therapy without more aggressive treatment within one month showed a slightly worse prognosis, only about 20 per cent being alive at the end of five years. In this series of cases, no patient received local therapy alone, although several had metastatic disease when they were first seen for definitive treatment. There is no statistical difference between the results of local therapy and those of wide surgical excision, but the groups are rather small in number. Between those cases treated surgically and those in which radiation therapy was also used there is considerable improvement with the addition of radiation therapy. Analysis of the

TABLE VI

FIVE YEAR SURVIVAL RATE

Type of Treatment	Total	Survived	Rate
Wide Surgery	42	11	26.2%
Local Therapy	71	14	19.7%
Radiation Therapy	121	50	41.3%
Total Cases	234	75	32.0%

Standard Error ±10.3 per cent.

TABLE VII

SURVIVAL AND SITE OF DISEASE

Site	−1 yr.	1–2 yr.	2–3 yr.	3–4 yr.	4–5 yr.	5–10 yr.	10–15 yr.	15– yr.	Total	Per Cent 1 year Mortality	Per Cent 5 year Survival
Lower Limb	20	13	6	8	3	17	1	3	71	28.1	29.5
Upper Limb	11	5	4	3	1	6	1	2	33	33.3	27.2
Head and Neck	21	12	3	6	2	14	13	3	74	28.5	40.5
Trunk	13	6	5	3	—	9	3	—	39	33.3	30.7
Female Genitalia	6	2	—	—	—	2	—	—	10	60.0	20.0
Brain	1	—	—	—	—	—	1	—	2	—	—
Unknown	3	1	1	—	—	—	—	—	5	—	—
Total Cases	75	39	19	20	6	48	19	8	234		

figures reveals that the standard error of deviation is as high as plus or minus 10 per cent. Even with the evident difference between 26 per cent and 41 per cent, therefore, one can but say that this is just statistically significant, and these figures cannot be advanced as definite proof of the advantage of giving radiation therapy to these cases. On the other hand, one cannot be certain that the patients in the different groups are strictly comparable. First there is a probability that the patients treated by surgery alone were in a relatively earlier stage of their disease than those in whom radiation therapy was added, for there would be a natural tendency to refer for postoperative irradiation only those patients in whom the surgeon did not feel confident of success from his treatment alone. Secondly, many of the more advanced cases were treated by irradiation and are included in that group. These considerations lend force to the suggestion that postoperative and palliative radiation therapy tends to improve the prognosis in this disease.

Table VII analyzes the survival of these patients according to the site of their primary disease. It would appear that lesions of the head and neck are accompanied by the best prognosis and this was also the finding of Cade[5] and Sylvén.[16] It is noteworthy that the mortality in the first year after diagnosis was established was the highest, approximately one-third of all patients failing to survive that period, and that a further 15 per cent died in the second year of their disease. Thereafter the death rate became somewhat less formidable.

Analysis of the five year survival rates according to the classification of Sylvén gave the following figures: Stage I, 51/102 = 50 per cent; Stage II, 22/93 = 23.6 per cent; Stage III 2/39 = 5.1 per cent. These figures for Stages I and II are higher than those previously reported and lend further support to the value of postoperative radiation therapy.

The over-all survival in this group was 32 per cent and this is comparable with the best figures published in a small selection from the voluminous literature on this subject (Table VIII). One of the series[2] which shows a higher survival rate refers only to the early, operable, or treatable cases. In other series melanoma of the choroid was included and this fact would tend to produce an improvement in the survival rate.

DISCUSSION

The natural history of malignant melanoma is quite variable, and even in apparently advanced cases, long-term survival is not infrequent. It is possible that the present series includes a high proportion of such cases, or that there was a relatively large number of patients in the early stages of the disease. Attempts have, therefore, been made to compare this series with

TABLE VIII

COMPARATIVE FIVE YEAR SURVIVAL RATES

Author	Year	Cases	Per Cent Survival
Ackerman[1]	1948	70	19.0%
Adair[2]	1936	400	14.5%
Adair[2] (operable cases)	1936	70	33.0%
Affleck[3]	1936	170	11.1%
Daland and Holmes[6]	1939	90	21.0%
Hall *et al.*[9]	1952	132	28.0%
Nathanson and Welch[10]	1937	128	32.5%
Pack *et al.*[12]	1947	862	9.7%
Preston *et al.*[14] (operable cases)	1954	47	28.0%
Scharnagel[15]	1933	56	33.9%
Sylvén[16]	1949	341	34.6%
Wright[20]	1949	70	28.6%
Total Cases		2,436	

others from the literature in regard to age, sex, body distribution and staging and it would appear that there is a fair degree of similarity.

The five year results of wide surgical excision alone are comparable with others reported in the literature, but when radiation therapy in adequate dosage was given to the areas of tumor involvement a higher survival-rate was obtained.

In this series there was a higher percentage of early cases which would improve the results, but when the material is broken down into stages, it is seen that the number of patients even in Stages I and II who survive more than five years is increased. The prognosis in Stage III remains negligible and the fact that 2 out of 39 patients in this group lived five years is probably fortuitous.

Although the evaluation of any method of treatment is difficult in such an unpredictable disease, it is felt that the improvement in survival rate over that reported by other authors, totaling nearly 2,500 cases, is indicative of a substantially beneficial effect from this method of treatment.

REPORT OF CASES

Two cases with exceptionally long-term survival are briefly reported.

CASE I. Miss E.O., aged twenty-four, was first seen at the Toronto General Hospital in February, 1933, with a malignant melanoma on the right elbow and satellite skin nodules surrounding the primary lesion. A wide local excision of the primary tumor was performed and 200 kv. radiation given to the area and to the local nodules. The dosage in this instance was 2,500 r in three treatments. For thirteen years she remained well but in April, 1946, enlarged lymph nodes were palpable in the axilla. A dissection showed them to be positive for melanoma and further radiation therapy was administered. A calculated tumor dose of about 4,000 r was given using three portals. In October, 1948, an enlarged lymph node was discovered on the right side of the neck but a block dissection of this area showed no melanomatus involvement. She was examined in March, 1955, at which time there was no evidence of local recurrence or of distant metastasis. She has remained well nine years since her last manifestation of disease and twenty-two years since the primary lesion was treated.

CASE II. Mrs. B.G., aged twenty-one, was seen in April, 1946, at the Johns Hopkins Hospital. She gave a history of a mole being present on the right shin for about two years. This she had repeatedly cut when shaving her legs and it had been cauterized, only to recur. Attempts had been made to excise the lesion locally on two occasions and in October, 1945, a course of local roentgen therapy was given elsewhere. The lesion recurred after both excisions. When seen in Johns Hopkins Hospital, there was a lesion on the right shin and an enlarged right inguinal lymph node. A wide excision of the tibial lesion with a graft from the right thigh and excision of the femoral and iliac lymph nodes were followed by a course of radiation therapy. A tumor dose of 3,500 r was delivered in four weeks using anterior and posterior portals. In November, 1946, a nodule was removed from the right buttock which showed no malignancy and she remained well until September, 1953. At this time a small nodule was removed from the area of the skin graft elsewhere but the histology of this lesion is unknown. In 1955, she became pregnant and in November gave birth to a normal baby boy without any complications. In July, 1956, a further tiny nodule was removed from the medial aspect of the right thigh distal to the donor area of the skin graft. This showed

"metastatic amelanotic malignant melanoma." In February, 1957, there was no evidence of further recurrence; the chest roentgenogram was clear and the patient remains well. It is now nearly eleven years since definitive therapy was undertaken for this lesion which had previously received grossly inadequate treatment.

SUMMARY

1. A five-year survival rate of 41 per cent has been achieved in a series of 121 cases of malignant melanoma treated by surgery and postoperative irradiation, or by palliative radiation therapy.

2. The surgery in Stages I and II consisted in most cases of a wide excision of the primary growth and the immediate lymph-drainage areas. Radiation therapy was delivered to all areas found to contain disease. It is submitted that the opinion that radiation therapy is valueless in this disease is based on experience with inadequate dosage.

3. The survival rates reported are higher than those of other series treated by surgery alone, although the material of this report appears to be comparable in all respects.

4. It is suggested that postoperative radiation therapy in association with wide excisional surgery is an adequate alternative to ablative and deforming operations.

The Johns Hopkins Hospital
Baltimore 5, Maryland

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CLINICAL EXPERIENCES WITH RADIOACTIVE MATERIALS*

By HARRY FOREMAN, M.D., WILLIAM MOSS, B.S., *and* BERNARD C. EUSTLER, B.A.
LOS ALAMOS, NEW MEXICO

PRESENT knowledge of the deleterious effects of internally deposited radioactive materials in humans has been obtained primarily from individuals with accidentally accumulated body burdens of isotopes of radium or thorium.[1,10,11,12] The following report presents a series of cases giving clinical information on several other particularly hazardous radioelements, *i.e.*, plutonium (Pu^{239}), americium (Am^{241}), and polonium (Po^{210}). These are all alpha emitters, the first two artificially produced and relatively recently discovered. Pu^{239}, with a half-life of approximately 24,000 years, is produced and used in considerable quantities and is of interest because of its nuclear power plant and weapon usage. Am^{241}, with a half-life of 500 years, is used primarily in research. Polonium, known for some time, recently has been extensively used as an ingredient in neutron sources. Po^{210}, with a half-life of 138 days, will probably be produced in large quantities as a toxic by-product in Thorium-Bismuth nuclear power plants.

Extensive animal studies have been made to determine body reaction to the presence of these elements. Pathologic effects observed for plutonium and americium are similar to those of radium.[2,14,15] Polonium in high dosage gives a clinical picture similar to "acute radiation syndrome."[4]

To date there has been no report of a human having received a sufficient quantity of any of these isotopes to produce demonstrable injury. The cases described below are reported here because:

1. They illustrate typical situations in which contamination accidents may occur.
2. They provide some of the first human excretion data on these isotopes (to be reported in the literature).
3. They document current techniques for evaluation and care of personnel contaminated by radioactivity.
4. It was possible to test the efficacy of therapeutic agents for hastening excretion of the isotopes in these cases.

REPORT OF CASES

CASE 1. *Americium.* This case involved a skilled radiochemist who, at the time of the accident, was working with a very "hot" mixture of Am^{241}, Am^{242}, Cm^{242} and associated fission products contained in a quartz ampule. A gamma-ray meter held 6 inches from the ampule read 150 r/hr. This mixture had been obtained by irradiating 5 mg. of Am^{241} in a high neutron flux pile. Just as the ampule was about to be opened (for reasons still undetermined), it exploded, forcing the contents over the top of the lead shield in front of the working space and spraying his face and hair. Almost immediately he scrubbed thoroughly with soap and water, but even after thorough washing there remained "hot" spots over his forehead, cheek and upper lip that went off-scale on the alpha meter and that read over 20 mr/hr. on the beta-gamma meter. He was taken to the hospital where physical examination revealed only minor abrasions over his forehead and in the mucous membranes of his mouth and nares.

The first urine sample, obtained approximately three hours after the accident, assayed 2 to 3 d./min./cc. The next urine sample, one to one and one-half hours later, showed an even higher count. This rising count strongly indicated that he had accumulated a body burden of radioactivity, probably through the abraded areas on his skin and mucous membranes and possibly by inhalation. Undoubtedly, some material was swallowed since gastric washings assayed over 1000 d./min./cc.

It was decided to attempt therapy, *i.e.*, to use a means to accelerate the excretion of the radioactive material. Calcium ethylenediaminetetraacetate (Ca EDTA), one of the current drugs recommended for this purpose,[5,6,7,16] was administered intravenously in 2 gm. doses in

* Work performed under the auspices of the United States Atomic Energy Commission.

250 cc. saline solution twice a day for five days, starting eight hours after the accident. A blood sample drawn at the time treatment was started assayed 3 d./min./cc. For the first two days the patient was hospitalized for observation and to assure full collection of urine and feces. He was ambulatory at all times and was able to help with the monitoring and to take full precautions to prevent contamination of hospital equipment. During his hospital stay, the remaining "hot" spots on his skin and hair were removed by repeated scrubbing with a mixture of detergent and Ca EDTA solution.

Shortly after admission to the hospital, a series of laboratory tests were run to serve as a base line against which to compare changes which might result from the radiation exposure or possibly from the use of the drug. These tests included a complete blood cell count with a platelet count, complete urinalysis, serum proteins, serum calcium and phosphorus, serum alkaline phosphatase and prothrombin time. Urinalysis was repeated daily while treatment was going on. Hematologic tests and serum chemistry tests were repeated in a week and after a month. No significant changes were ever noted.

After leaving the hospital, treatment was continued at the same dosage level for three more days on a come-and-go basis in the first-aid room. Following that, Ca EDTA was given only as a diagnostic aid, at times indicated in Figure 1.

The results of urine excretion assays are presented in Figure 1, expressed as disintegrations of americium* per minute per twenty-four hours (d./min./24 hr.) During the first twenty-four hours, urine excretion was about 11,000 d./min., a surprisingly high amount, indicating either a high degree of effectiveness for the treatment or the presence of a dangerously high level of activity in the body. Fortunately, the former turned out to be true. The excretion level remained high in the first few days and dropped abruptly with cessation of treatment, rising again sharply when treatment was reinstituted. One month after the accident, urine excretion levels had fallen to approximately 0.5 d./min./24 hr., the lowest level of significant

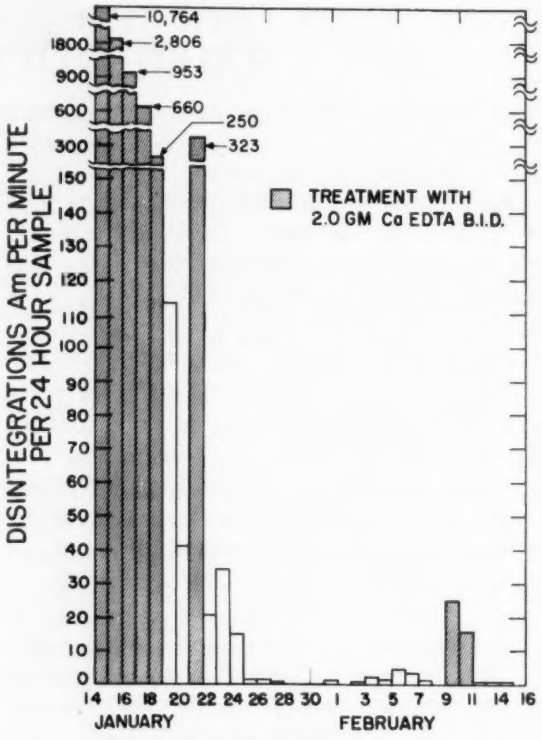

FIG. 1. Effect of Ca EDTA on urinary americium excretion.

detection by the analytical procedure used. Urine samples were assayed monthly from then on. The assays ranged from 0.12 to 0.30 d./min./24 hr., values which would not be taken to indicate with any certainty the presence of any americium internally. One could not distinguish these urine samples from others obtained from individuals who had had no americium exposure. Approximately one year after the accident, he was given an additional trial of Ca EDTA. The urine excretion level rose from a pretreatment level of 0.2 d./min. to 4.2 d./min. on the first day of treatment, then to 2.4 d./min., and 1.6 d./min. on subsequent treatment days and dropped to 0.3 d./min. the day after treatment was stopped. Ca EDTA, used in this fashion, served as a diagnostic aid to demonstrate the presence of a body burden of activity not otherwise detectable.

Fecal samples were collected for the first seven days. The results of assay of these samples are given in Table 1. The very high fecal excretion in the seven days (over 80,000 d./min. of americium) was undoubtedly in a large measure due to material that was swallowed and excreted, rather than material which had

* Because of the short half-lives of most of the isotopes in the contamination mixture, the only appreciable activity detectable in a few days after the accident was that associated with Am^{241} and Cm^{242}. Pulse height analysis of the activity in the urine showed the Am:Cm ratio to be 16 to 1. Since the hazard from curium is almost the same as that from americium, no great error was introduced by considering all of the activity to be americium.

Table I

AMERICIUM FECES EXCRETION

Date	Disintegrations per Minute of Americium per Twenty-four Hour Specimen
January 14	14,800
15	41,000
16	19,000
17	1,541
18	2,105
19	1,710
20	438

actually gained entrance into the circulation and was being excreted through the bowel.

With the data at hand, it was possible to estimate the present body burden, the effectiveness of the treatment and the initial dose taken in. The calculation of the body burden was made by using an empirical excretion curve obtained from humans for plutonium and extrapolating to americium by use of a factor. The assumption was made that the treatment did not alter the slope of the excretion curve at times long after the treatment was stopped. The equation of the excretion curve for plutonium as given by Langham[8] is:

$$D_r = 435\ Ut^{0.76}$$

where D_r is the body burden in d./min., U is the urine excretion in d./min., on day t, and t is the time in days after the exposure. The factor for adapting the equation for use with americium was obtained from Carter and Langham's[3] study in animals, wherein it was shown that plutonium and americium urine excretory curves are approximately parallel and that at a given time, *i.e.*, thirty days, after the entrance of the isotope into the body, the urine excretion of americium is twice that of plutonium. With this information adapting the equation for use in americium cases was simple, namely:

$$D_r \text{ (americium)} = 1/2 D_r \text{ (plutonium)}$$
$$= 1/2\ (435\ Ut^{0.76})$$

In the case under discussion, at thirty days the americium urine excretion, U, was 0.45 d./min. Putting this datum into the equation gave a body burden of 1,350 d./min. at thirty days.

The calculation of the amount of activity entering the body was made as follows. Langham (again from human plutonium studies) found the amount of plutonium remaining in the body at thirty days after acute exposure is 96.3 per cent of the initial dose. For americium, using the same factor as above, this would be approximately 92.5 per cent. With a body burden of 1,350 d./min., the corresponding initial dose is 1,460 or approximately 1,500. However, in the present case, treatment resulted in the excretion of an additional 16,000 d./min. (this neglects the 150 or so d./min. which would have been excreted normally, but this is negligible compared to the 16,000), so the actual initial dose must have been 1,500+16,000 or approximately 17,500 d./min.

The efficacy of the treatment can be judged by comparing the present body burden with that which would have resulted had no treatment been given. With an initial dose of 17,500 d./min., the amount remaining in the body at thirty days (without treatment) would be the initial dose (17,500) minus the amount excreted (0.075 ×17,500), namely, 16,200 d./min. This value compared to 1,350 indicates the treatment was decidedly efficacious. As a result of the treatment the body burden is less than one-tenth of what it would have been had treatment not been instituted.

Case II. *Plutonium.* This case concerns a forty year old woman technician,* who at the time of the accident was working with a plutonium solution in 1 N HNO_3 that assayed approximately 2×10^6 d./min./cc. The flask broke and a jagged edge of the broken contaminated glass cut her across the base of the thumb through a rubber glove. The first-aid treatment

* A preliminary report of this case was presented to the Section on Preventive and Industrial Medicine at the 103rd Annual Meeting of the American Medical Association in San Francisco, 1954, and published in the *A. M. A. Arch. Ind. Hyg. & Occ. Med.*, 1954, *10*, 226.

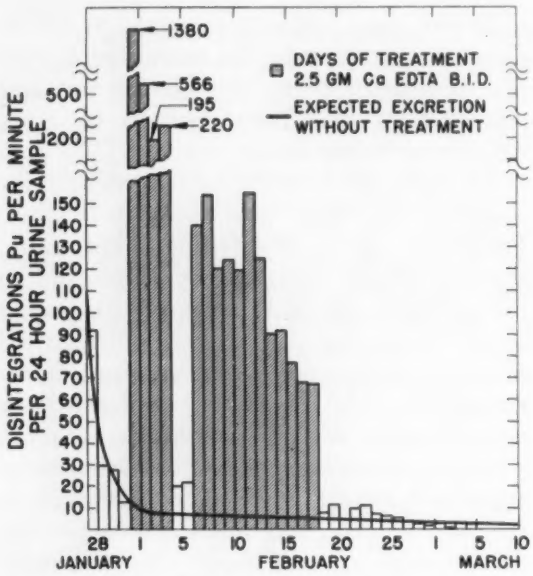

FIG. 2. Effect of Ca EDTA on urinary plutonium excretion.

consisted of cleansing the wound area with soap and water and stopping the profuse bleeding with a couple of sutures and a small pressure dressing.

From the conditions of the accident, it did not seem likely that any appreciable radioactive material had entered the wound. However, an alpha meter passed over the surface of her hand indicated a few "hot" spots as high as 1,000 c./min., after the initial cleansing. It was decided to collect urine in an attempt to learn how much, if any, plutonium had gained entrance into the body. The first day's collection of urine assayed 90 d./min. There was a possibility that this sample was contaminated, as occurs not infrequently in the first urine samples collected after an accident. However, subsequent collections on the following days showed continued excretion of measurable amounts of plutonium. It was apparent that a small amount of plutonium had been absorbed from the wound and, therefore, it was decided to give her Ca EDTA.

Before starting the treatment, the wound area was excised. The excised specimen assayed 1,500 d./min., a very small amount. Ca EDTA was given in 2.5 gm. doses in 500 cc. of saline solution by slow intravenous drip twice a day for four days, stopped for two days, and then given again under the same regimen for twelve days. The first day of treatment brought forth an unusually high excretion; the count jumped from a pretreatment level of 12 up to 1,380. As seen in Figure 2, on subsequent days under treatment, the output continued high. When treatment was stopped, the level dropped sharply and rose again with renewed treatment.

Toward the last of the second course of treatment, the patient began to develop symptoms, first a nonspecific malaise, then a backache and finally urinary frequency and nocturia. It was suspected that the symptoms might be related to the treatment. Treatment was stopped and an attempt was made to learn the cause of her illness. There were no unusual findings on physical examination. The standard blood chemistry and blood morphology studies gave normal values. Urinalysis, however, showed 2+ albumin, many fine granular casts, occasional red blood cells and a few white blood cells. Urine culture was negative. The signs and symptoms cleared quickly with rest. In two or three days, the symptoms were gone and by the fourth day, the urine was entirely clear and the patient appeared well.*

Calculation of the body burden was made similarly to the way in which the body burden was calculated in the americium case described above. Forty days after the accident, the urine excretion level averaged 1.95 d./min. of plutonium per twenty-four hours. At this excretion level, the equation yields a body burden of 14,000 d./min.

As seen from Langham's data, under ordinary conditions, the body burden of plutonium at thirty days is 96.3 per cent of an initial acute dose, which in this case would give

$$\frac{14{,}000}{96.3} = 14{,}540 \text{ d./min.}$$

To obtain the actual initial dose, the amount excreted under treatment must be added to this value, giving 14,540+4,500= 19,040 d./min. With an initial value of this magnitude, the body burden at thirty days without treatment would have been

* As a result of this case, an extensive toxicology study of Ca EDTA was undertaken in rats. It was found that when the drug is given repeatedly and in sufficiently high doses, a reversible tubular nephrosis could be produced. The results of these studies are reported in the *J.A.M.A.*, 1956, *160*, 1042. These findings make it quite likely that the symptoms seen in the case above were related to the drug.

19,040 − 3.7 per cent of 19,040 = 18,366 d./min. The actual body burden was 14,000 d./min. or approximately 76 per cent of this. The difference of 24 per cent is an index of the effectiveness of the treatment. It is likely that had the drug been started almost immediately after the accident instead of five days later, the treatment would have been even more efficacious.

Case III. *Plutonium.* This case was a more complicated one. The individual involved had been working with plutonium in various forms for a number of years and had had several minor contamination accidents. He was slowly accumulating plutonium internally as evidenced by a slowly rising urine count over the years. It was just about decided to remove him from his job and place him on work away from plutonium when he had this rather serious accident.

The accident occurred while he was working in a drybox used for processing plutonium residues. He was placing rubber tubing over the outlet of a suction flask when the tip broke and he was cut across the ball of the thumb. The flask was highly contaminated with plutonium in various forms, the nitrate, fluoride, oxide, *etc.* Surface counts of both the glove he was wearing and the skin about the wound were off-scale on the alpha meter.

He was taken to the hospital where the wound area was immediately excised. Analysis of the tissue yielded 850,000 d./min. The removal of this tremendous amount amply justified our practice of excising all potentially contaminated wounds.

Treatment with Ca EDTA was started about one hour after the accident. Results of the urine assays are shown in Figure 3. The urinary excretion of plutonium for the first day (from about 4:30 in the afternoon, when the accident occurred, until the following morning) was 80 d./min. It was expected from the conditions of the accident that there would be a tremendous excretion, but surprisingly enough, the value was low. Then, instead of dropping as had happened in previous cases, the excretion rose on subsequent days. This rising level was interpreted to mean there was still plutonium left at the wound site that was slowly feeding into the blood stream.

After four days, treatment was stopped. The reasoning was as follows. Only a little over 1,000 d./min. had been put out in the four days. If

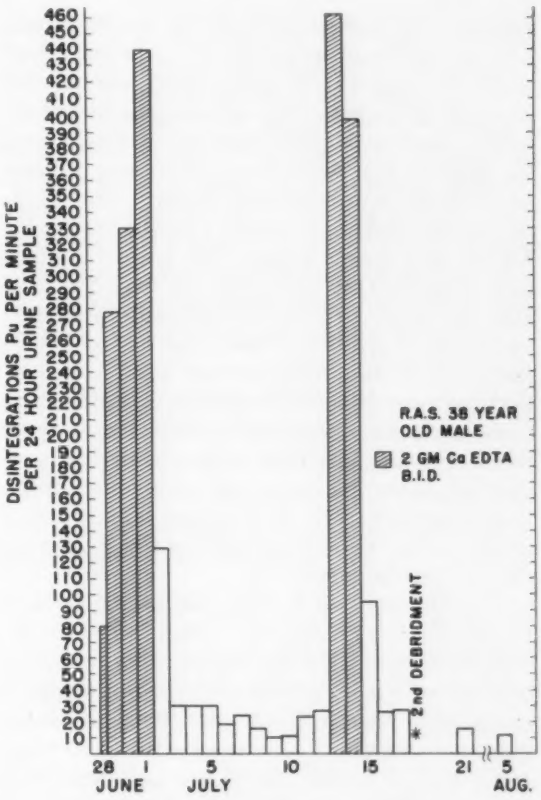

Fig. 3. Effect of Ca EDTA on urinary plutonium excretion.

the treatment was very effective, *i.e.*, this excretion level represented a high percentage of his body burden, then he must not have had much plutonium in him. The other alternative was that the low level of excretion was due to the fact that the treatment was not being very effective. In either case, it was advisable to stop treatment. With the stopping of the drug, the urinary plutonium excretion dropped to 27 d./min./day and stayed about this level for five days. This gave further confirmation to the impression that an intramuscular source was feeding into the blood stream since the excretion level would have been expected to drop sharply at this time had a single acute exposure occurred. Another two days of Ca EDTA treatment was given and again the excretion went up, this time even higher than on the first day. It was decided to excise more of the wound area. The second tissue piece assayed 30,000 d./min. The effect of the excision was immediately manifest in the urine. The excretion began to fall and dropped steadily to a level of 9 d./min./day about one week after the second

excision. By one year after the accident, the level had fallen to approximately 4 d./min./day.

At the time the excretion level was on the order of 9 d./min./day, it was possible to do further studies to gain more information about Ca EDTA and plutonium excretion. In one such study, a comparison between orally administered and intravenously administered Ca EDTA was made. A three-day trial of 2 gm. a day of Ca EDTA was made for each mode of administration. The oral treatment produced no change in excretion above the control levels. Intravenous administration resulted in a tenfold increase in urinary plutonium excretion. Fecal excretion assays were also made at these times. Intravenous administration of the drug did not alter the fecal excretion. The feces: urine excretion ratio was approximately 1 to 1 in the control period and did not change during the oral treatment period.

The net increase in excretion brought about by the Ca EDTA was not significant. The administration of the drug was of value primarily because of the diagnostic information it gave, namely, in pointing out the residual intramuscular deposit. The apparent ineffectiveness of Ca EDTA in this case might well have been because of the very low blood levels of plutonium present at any one time, *i.e.*, that small amount of plutonium that was being fed slowly from the intramuscular site into the circulation.

Using the same mode of calculation as described above, it is estimated that the body burden at seventy days after the accident was approximately 50,000 d./min.[9]

CASE IV and CASE V. *Polonium.* These cases involved two young physicists whose cases are so similar that they can be described together. Both were exposed at the same time in the same accident.

The details of the exposure were as follows. The two men had been working with a 25-curie mock fission neutron source contained in a graphite pile, when it was noticed that the neutron flux was about 5 per cent higher than expected. While they were investigating the cause, the apparently already defective Po-Be source ruptured and sprayed alpha active material over the source room. The cause of the rupture was judged to be a buildup of hydrogen and oxygen which had resulted from irradiation of the moisture collected in the capsule.

The men left the room almost immediately. Essentially all of the exposure to the activity occurred during the few minutes while the men were in the source room right after the accident. On coming out of the room, their clothing and exposed parts of the body, the face, neck and hair had counts ranging up to 20,000 c./min. of alpha activity. After a shower and change of clothing, the only appreciable activity remaining in both cases was on the upper lip. This activity persisted for several days, even after repeated scrubbing with detergent and water. Apparently it was due to the deposition of exhaled polonium.

On physical examination, no cuts, abrasions or any evidence of injury were found. Collection of urine and feces samples was started and a series of laboratory tests was run as a base line against which to measure any possible future changes which might occur from irradiation. The tests included a complete blood cell count, platelet count, sedimentation rate, bleeding and clotting time, serum phosphatase, prothrombin time, nonprotein nitrogen, serum proteins and urinalysis. Tests were repeated on alternate days for the first week, then weekly for the rest of a month and at the end of the second month. No changes from the normal were noted in either case. The men never ceased their normal activities, except that they were kept away from radiation sources for several weeks.

It was possible to follow total excretion (urinary and fecal) in the individual who received the largest dose (as manifested by excretion rates). In the second case, only urinary excretion was closely followed. The results are presented in Figure 4. At the beginning of the third week, a three day course of Ca EDTA, 4 gm. daily in 2 divided doses by slow intravenous drip, was given to one of the men. There was no change in excretion rate.

From simple inspection of the curves, it is immediately apparent in an inhalation exposure such as these that excretion is predominantly via the feces. For the first week after exposure, fecal excretion was 2 to 3 orders of magnitude greater than urinary excretion. At later time periods, urine and feces contribution tended to approach each other, but even at five months, the polonium level in the feces was at least 10 times greater than in the urine. The plot of fecal excretion data on a semi-log scale showed that there are two definite phases of fecal excretion, an early one occurring at a half-time of 0.6 days and a later one at a rate characterized by a half-time of 19.6 days. The first excretion phase

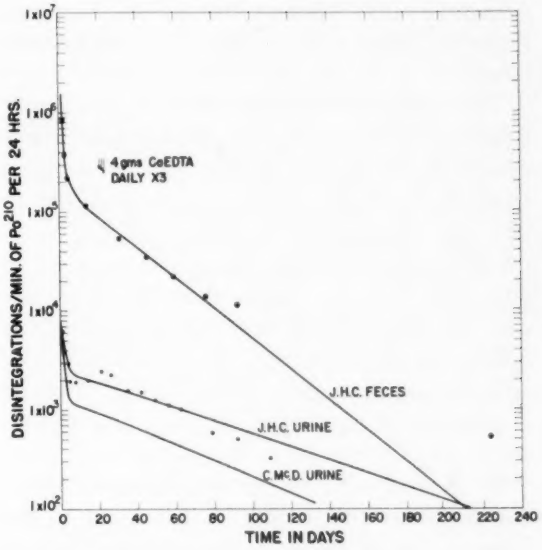

FIG. 4. Effect of Ca EDTA on urinary polonium excretion.

probably represents swallowed activity brought up from the pharynx and major bronchi, plus the polonium that was swallowed initially. The activity appearing in the second phase was probably polonium which was brought up from the lower respiratory tract by ciliary action and swallowed, as well as material which had gained entry into the systemic circulation across the lung alveoli and intestinal wall and was excreted through the bile.

Urinary excretion plotted on a semi-log scale likewise was resolved into two components in both cases, an initial component with an approximate half-time of 0.75 days and a later component with a half-time of 47 days in one case and 37 days in the second. The first phase was probably due to polonium entering the systemic circulation across the alveoli and gastrointestinal tract, and the second phase, material being returned to the blood stream after initial deposition in tissue sites.

Unlike the situation for plutonium and americium, the calculation of body burden at any given time after an acute exposure for polonium is not particularly meaningful because the body burden changes rapidly with time and in a relatively short time becomes insignificant. Of much more importance is the calculation of the initial dose, because from this value and the excretion rates one can obtain an idea of the internal radiation dose received as a result of the exposure.

The length of time for the body burden to fall to essentially zero was estimated by extrapolation of the excretion curves to the time when excretion levels were insignificant, *i.e.*, below 1 d./min./day. In the case where both feces and urine data were available, the feces excretion was calculated to become insignificant at three hundred and forty days and urine excretion about three hundred and seventy days. Actual assays of excreta at one year after exposure verified this. The initial dose received was estimated by summing up the total excretion from time of exposure until one year later. The general equation for the excretion curves is:

$$E_t = D_1 e^{-k_1 t} + D_2 e^{-k_2 t}$$

where E_t is the twenty-four hour excretion at time t, D_1 and D_2 represent the amount of material present initially, and k_1 and k_2 the rate constants for the two different phases of excretion. Integration of this equation from zero to time t sums up the excretion during that time. The expression for the integration is:

$$\int_0^t (D_1 e^{-k_1 t} + D_2 e^{-k_2 t}) = \frac{D_1(1-e^{-k_1 t})}{k_1} + \frac{D_2(1-e^{-k_2 t})}{k_2}.$$

Substitution of numerical values from the excretion curves with $t = 365$ days and with appropriate corrections for radioactive decay gives the following:

Total Fecal Excretion

$$= \frac{6.89 \times 10^6 (1 - e^{-1.17 \times 365})}{1.17} + \frac{1.74 \times 10^5 (1 - e^{-0.04 \times 365})}{0.04}$$

$$= 10.24 \times 10^6 \text{ d./min., or } 4.65 \ \mu\text{c.}$$

Total Urine Excretion

$$= \frac{8.81 \times 10^3 (1 - e^{-0.97 \times 365})}{0.97}$$

$$+\frac{2.8\times10^{3}(1-e^{-0.02\times365})}{0.02}$$

$$=1.49\times10^{5}\text{ d./min., or }0.067\ \mu\text{c.}$$

The total excretion, the sum of the urinary plus fecal excretion, was 4.65+0.067 or 4.72 μc. This essentially represents the amount of activity initially entering the body. The determination of the radiation dose delivered to the various organs in the body following the inhalation of this quantity of Po^{210} was not possible because of lack of information on the distribution of the activity in the body. However, by the use of certain assumptions, it was possible to calculate the maximum possible dose to the organ most likely to have received the largest dose, namely, the lung. The total energy delivered to the lung by the 4.72 μc of Po^{210} in terms of mev., using the fecal excretion data, was:

$$\Big[5.89\times10^{6}\Big(\begin{matrix}\text{Portion of initial activity}\\ \text{excreted in phase one}\end{matrix}\Big)\times1.23\times10^{3}\Big(\begin{matrix}\text{Mean life of phase}\\ \text{one in minutes}\end{matrix}\Big)+4.35\times10^{6}\Big(\begin{matrix}\text{Portion of initial activity}\\ \text{excreted in phase two}\end{matrix}\Big)\times3.6\times10^{4}\Big(\begin{matrix}\text{Mean life of phase}\\ \text{two in minutes}\end{matrix}\Big)\Big]5.3\Big(\begin{matrix}\text{Energy of Po}^{210}\\ \text{alpha in mev.}\end{matrix}\Big)=8.68\times10^{11}\text{ mev.}$$

Converting this to rep, assuming uniform distribution throughout the lung, one obtains:

$$\frac{8.68\times10^{11}}{10^{3}\text{ (nominal wt. of lung)}\times5.18\times10^{7}\text{ (mev./gm./rep)}}=16.6\text{ rep}^{*}$$

This result does not include the contribution made by the polonium which was eventually excreted in the urine. At most, however, this could be only 1 per cent of the total.

The gastrointestinal tract is the only other system of organs that might have received a radiation dose even approaching that of the lung, but it is not possible to estimate this, except to guess that the overall dose was certainly far less than that to the lung. On the basis that 0.004 of the amount of polonium in the lung reached the spleen (see Handbook 52),[13] the dose to the spleen (the so-called critical organ) can be estimated to be negligible, *i.e.*, less than 1 per cent of the dose to the lungs.

In the second case, an estimate of the initial dose and the total radiation dose to the lung can be made by merely comparing the urine polonium output (the only available data) with that of the first case. Results of approximately one-half that of Case IV are obtained.

* This calculation does not include any factor for any unusual RBE (relative biological effectiveness) for the polonium alpha particles, but in all likelihood only a small error is introduced by this simplification.

SUMMARY

Case reports are presented on 1 individual who received an internal dose of Am^{241}, on 2 individuals who accumulated Pu^{239} internally, and on 2 individuals who received a body burden of Po^{210}. The urinary excretion of the isotopes was followed closely over a long period of time in all cases, and the results of the assays are reported. In 2 cases, the assays on feces are also presented. The results of attempts to accelerate excretion of the isotopes are presented. A procedure for evaluating the initial dose, the body burden at given periods of time, and the effect of treatment is given. The technique for estimating the dose received from the polonium exposure is described and the dose received evaluated.

Harry Foreman, M.D.
Los Alamos Scientific Laboratory
P.O. Box 1663
Los Alamos, New Mexico

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BRACHYTHERAPY*

By MARSHALL BRUCER, M.D.†
OAK RIDGE, TENNESSEE

THERE is a story that brachytherapy was invented in 1901 when Pierre Curie gave a small tube of radium to a Dr. Danlos with the suggestion that maybe it could be inserted into a tumor. Dr. Danlos did not report his results for about four years, but apparently he acted on the suggestion at once. Completely independently, about two years after Pierre Curie made his suggestion, Dr. Alexander Graham Bell made a similar one. He wrote a letter to the editor and in the August, 1903, issue of the *Archives of the Roentgen Ray* (Vol. 8, p. 64) we find,

"*. . . but there is no reason why a tiny fragment of radium sealed up in a fine glass tube should not be inserted into the very heart of the cancer, thus acting directly upon the diseased material.*"

There was a lot of concern about radium in the early 1900's. During a century of intellectual development, the basic sciences of physics and chemistry reached a peak of perfection and the applied sciences of physiology, biochemistry, and bacteriology were born. Men turned from science to engineering. Biochemistry became internal medicine; bacteriology became pasteurization; chemistry went into production; and physics, always the laggard, flowered into the electric light bulb, the steam engine, and the airplane. Science died about 1900 and engineering took its place.

Medicine is one of the great engineering disciplines that grows out of physics and chemistry. It is understandable to the layman. One of the minor gadgets of physics, the roentgen-ray tube, caught the public's fancy and radiation became Sunday supplement science. A more deep-rooted anomaly in chemistry, the radioactivity of elements, was discovered at the turn of the century; and engineers, mechanical and medical, looked for an application. For example, in the April, 1903, editorial in the *Archives of the Roentgen Ray* entitled "What Is All This about Radium?" (Vol. 7, p. 116) the suggestion was made that:

"*if we had plenty of (radium), we might paint London with calcium sulfide, put radium in the street lamps, and get a mild moonlight everywhere, while saving on gas and electricity. But people careful of their complexions might object to its effect upon the cuticle. No; it cannot be said at present to be of any extensive practical utility. But it is only a baby, . . . and we are very likely to hit upon something . . . that just gives the hint required to make some other pieces of knowledge useful.*"

Radium had an advantage, especially in medicine, that made it appear superior to roentgen ray. Many physicians still alive remember the rooms full of equipment that went along with a roentgen-ray machine. This was disconcerting to the physicians who practiced radiology during its early history. In the March, 1902, *Archives of the Roentgen Ray* (Vol. 6, p. 70) Dr. E. W. H. Shenton made a statement that could still be the watchword of designers of therapeutic equipment:

"*Furthermore I would earnestly ask you to consider the desirability of introducing greater simplicity into methods and apparatus doing away with a want rather than creating one.*"

The radium therapy ideas that were just being thought of at the turn of the century seemed to be perfect answers to the complexity of radiation equipment.

Even before physicists were positive that radium and roentgen rays were really variations of the same thing, physicians realized that the results were similar; and radium was undergoing clinical trial long before it was reported in the medical literature. For

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† Chairman, The Medical Division, Oak Ridge Institute of Nuclear Studies, Inc., Oak Ridge, Tennessee. (Under contract with the United States Atomic Energy Commission, Oak Ridge, Tennessee.)

example, in the July, 1903, "Notes and Abstracts" of the *Archives of the Roentgen Ray* (Vol. 8, p. 34) the statement appears:

"Reports, apparently authoritative, have been received from Vienna to the effect that at a recent meeting of the medical society of that city two cases were presented in which recurrent malignant growths had been healed by means of radium."

More physicians used brachytherapy than wrote about it.

The treatment of tumors with radiation, however, was not haphazard. It was being studied and many of the physicians who were studying the use of radiation in therapy, even at this early date, were critical as well as ecstatic about its results. For example, in the December, 1903, *Archives of the Roentgen Ray* (Vol. 8, p. 111) Dr. H. E. Gamlen in England made the statement:

"The attempt to treat cancer by means of X rays has been somewhat discouraging."

He was not the first to make this statement nor was he the last. One of the enjoyable things about reading the history of roentgen therapy is the complete honesty of physicians in reporting the results of their cases.

But their candor and discouragement did not stop physicians from trying to use various kinds of brachytherapy devices. For example, in July, 1908, Dr. C. T. Holland summarized previous work on thyroid disease in the *Archives of the Roentgen Ray* (Vol. 13, p. 39) with these examples: Abbe reported in 1905 that he had opened the hypertrophied middle lobe of the thyroid gland and introduced a sterilized glass tube containing 10 centigrams of radium. Dominici reported that he tried placing a cloth impregnated with radium around the neck of a patient but that he separated this from the skin by protective material that arrested the alpha and beta rays. Dominici already knew in 1905 that this was what caused the main damage to the skin.

A point that will be brought up in any discussion of brachytherapy devices is that of protection. At the turn of the century this topic was much more important than it is today. In an unsigned editorial in the July, 1908, *Archives of the Roentgen Ray* (Vol. 13, p. 36) the writer states:

"We would draw attention . . . to the unfortunate frequency of grave injuries which have befallen employees and lay assistants engaged in the manufacture and use of X-ray tubes. Amongst those who were employed in the early days of roentgenology, before any adequate means of protection had been devised . . . it is almost impossible to find anyone who has not been more or less seriously injured."

Protection from radiation is not a subject confined to post-World War II scientists. The necessity for protection was discovered almost with the first roentgen-ray tube. The subject was amplified when radium came into being, and much of what we now know about protection was thoroughly appreciated by physicians before 1910.

The same kind of statement can be made about everything connected with brachytherapy. Almost all the ideas that have been suggested recently for the use of radioisotopes in brachytherapy devices were suggested previously by the physicians who were playing with radium. For example, in the July, 1910, issue of *Archives of the Roentgen Ray* (Vol. 15, p. 74) there is the comment:

"Dr. Abbe of New York has a very ingenious method of introducing radium into the substance of a tumor. After opening up the tumor he makes an incision into its substance and inserts a number of celluloid tubes about the size of a clinical thermometer . . . the wound is then closed, leaving the ends of the celluloid tubes protruding. It is easy then to introduce the glass radium capsule into each tube successively, and retain it there as long as desired . . ."

Radium solutions were suggested that could be applied directly to the bladder or in balloons inserted into cavities. Beads, seeds, plaques, and applicators of all sizes and shapes were suggested and even tried. If one substitutes the word "radium" for the word "radioisotope" then almost every

idea that has been published as a new discovery since 1946 has its counterpart before 1910.

However, radium was excessively expensive. Radioisotopes are now inexpensive. Radium gives one energy spectrum. With radioisotopes we now have a choice of almost any radiation spectrum. Radium for all practical purposes was a permanent material. Radioisotopes give us a choice of half lives. The difficulties of working with radium (primarily the expense) caused a decrease in interest in brachytherapy. Most of the difficulties of working with radium have now been overcome with radioisotopes and it is time to renew some of the enthusiasm the early workers had in devising therapeutic methods. In addition to the advantages that radioisotopes furnish over radium, there is also the one tremendous advantage that radioisotopes can build on a foundation of fifty years of clinical experience with radium. This is probably the chief advantage that the 1957 therapist has with radioisotopes over the 1910 therapist with radium.

PROTECTION

A number of items should be considered when thinking of the design of brachytherapy devices. Probably the first and the most important of these is radiation protection. This protection must be given to the machinist who manufactures the device and to the loader or the man who is preparing the device for use by the therapist. The protection of the therapist is important, and the protection of the patient must be considered.

Although there is a great range of choices of artificially produced radioactive isotopes, the problems of the man who is making devices determine the initial cost of brachytherapy. One of the primary reasons for the decrease in intellectual interest in devising brachytherapy methods was the cost of radium before 1910. Any item that can be thought of by any therapist can probably be made. However, there will be a cost involved in manufacturing each device. We have adopted as a general rule that any brachytherapy device costing more than a similar radium device is not as good as a radium device. For example, it is possible to make a cesium therapy needle, and this has already been done repeatedly in Oak Ridge. The cesium, however, must be loaded and welded into the needle behind shields of considerable thickness. Welding machines that can accomplish this are available in Oak Ridge, but the cost of a "hot" loading is enormous. It would probably be more economical to use the europium 152 isotope for the same purpose. Stable europium is loaded into the needle and then the whole needle is put into the reactor and the isotope europium 152 is produced. All the machining and welding is done in the "cold" state and the cost is simply that of an ordinary machine shop. The use of reactor-produced isotopes is probably cheaper than the use of fission products in brachytherapy devices. This is true when the problem of the protection of the machinist from radiation is taken into consideration.

The conventional Ernst applicator brings up another protection problem. In the Ernst applicator there is almost an infinite variety of source arrangements; however, somebody must load these sources, and although this is a relatively simple procedure, the man who does the loading receives a radiation exposure. With the cost of isotopes so low, it is possible that Ernst-type applicators could be made with permanent loadings and thus do away with exposure to the loader.

The therapist probably receives the greatest undesirable radiation exposure when he inserts needles, seeds, and beads into place. The use of a device suggested at the University of Chicago in which the surgeon sews tubing into place and later fills it with a liquid isotope from a fully protected cart is one way of avoiding this problem. A whole range of artificially produced radioactive isotopes can be pro-

duced in liquid form and could be used in this manner. Disadvantages, however, accompany the advantage of low radiation exposure to the therapist.

The problem of the exposure to the patient is also in a sense a protection problem. Only a small volume of the tissues of the patient is being irradiated purposely and therapeutically. All the irradiation of normal tissues could be considered undesirable. With radium (and other high-energy gamma sources) this undesirable exposure of the patient can be significant. With many radioisotopes the energy levels can be selected to effectively irradiate anywhere from millimeters to many centimeters of tissue depth. The therapist now has some control over the undesirable exposure to the patient.

CONTAMINATION

In considering the undesirable exposure to the patient, there is a problem of contamination. Two kinds of contamination are significant. The first is the contamination with the element itself and this can be called chemical contamination. The second is contamination of the field of radiation with electrons.

The first problem, that of chemical contamination, is an obvious one. When radium was inserted in glass tubes, there was always the possibility of breakage. The radium element and its decay products were, in a sense, injected into the body by this breakage and the radium entered into the body metabolism. When radium needles were redesigned and constructed of steel or platinum-iridium, this kind of breakage decreased in importance. However, it is still possible and occasionally it does occur that the metal tubes are bent, their seal is broken, and radon and even radium can leak out into the tissues. If a fission product, such as cesium, is put into a brachytherapy device in the chemical form of a powder or liquid, the seal becomes exceedingly important. It is very difficult to construct any sealed source that has no "leakage." With very powerful beta emitters metal is not necessarily a good seal. Leakage of the element can go directly through even a fairly thick metallic wall. When thin metallic walls that would ordinarily be considered to be a large particle seal are used, we must still consider the porosity of the metal. When sources such as pure cobalt wire are irradiated in a nuclear reactor and are plated with an inactive metal such as nickel, porosity of the plating can lead to chemical contamination. With long-lived radioactive isotopes prepared in any chemical form, the problem of devising a sealed source is difficult. There is probably no such thing as a theoretically perfect seal except in very large containers, and the term "sealed source" has many different meanings. For the purposes of the ORINS program a sealed source has been defined as a source that results in a leakage of less than a few times the natural background of the detecting device.

Therapists have learned to live with electron contamination. When high-energy gamma photons interact in the metal container that makes up a needle, the interaction often produces a high-energy electron. This means that, no matter how thin or thick the metal, a certain number of electrons are produced in the capsule itself. An electron contamination is always close to the surface of a brachytherapy needle. Therapists have learned to work with platinum-iridium radium needles. These are designed to have a thickness at an optimum level. The largest proportion of electrons originating in the radium are shielded out of the gamma field and the smallest number of Compton interaction electrons are produced by the metal. This electron contamination can be controlled by making the capsules of a medium weight metal such as iron, cobalt, nickel, copper, or zinc. However, since the density of these metals is lower than the density of the heavy metals, the brachytherapy device automatically becomes thicker. Where thick walls do not interfere, these metals

should be used. Where thick walls do interfere with the design of the brachytherapy device (such as in radium needles), only the high density metals can be used.

One set of brachytherapy devices has been designed specifically with these two contamination problems in mind. These devices are made of the Incoray alloy developed by the International Nickel Company. The Incoray alloy is made almost completely of medium weight metals. Electron contamination is reduced to a minimum. Incoray contains, in alloy form, a small amount (5 per cent) of cobalt. This is the only element included in the alloy that yields a long-lived gamma-emitting isotope. Since the beta emission from cobalt 60 is of low energy, even very thin devices will give maximum shielding to the electrons produced in the disintegration of the cobalt isotope. The alloy is very highly corrosion resistant. It is made up primarily of nickel (74 per cent) that is well tolerated by the body. After neutron irradiation the devices are washed in *aqua regia* to remove all the cobalt from the surface. This makes the Incoray alloy highly contamination resistant from the standpoint of radioactivity. Since Incoray is made of medium weight metals, the Compton interactions produce scattered electrons in almost negligible amounts. There are disadvantages to the Incoray devices but they do answer the problems of contamination.

HALF LIFE

The half life of an isotope helps determine its usefulness for brachytherapy. Many otherwise desirable isotopes have half lives measured in terms of seconds. These are obviously of little use to a brachytherapist. Radium has an ideal half life. For brachytherapy devices, as for all other isotope use, there is an acceptable half life when one considers cost, handling, specific activity, and all other practical factors. The lower limit of half life for medical usefulness is probably measured in a few days, but there is no real limit of practicality since this depends upon the setup used for making the brachytherapy devices. At the present time most devices are manufactured in one place and shipped to another. Radioactive gold has proved to be impractical in proportion to the distance it must be shipped from Oak Ridge. Therefore, the few-day limit is on the edge of impracticality. For brachytherapy devices one would like to have a long lived isotope such as cesium 137. However, this is a fission product. The problems of manufacturing and loading fission products keep them from being the perfect answer. Cobalt 60 is easily produced and is becoming a less expensive isotope as the years go by. The five-year half life is satisfactory to a therapist intensely interested in brachytherapy; however, five years is a fairly short half life, and the costs of maintaining the bookkeeping system and health physics calibrations and surveys are a significant part of the problem. Europium 152 has been introduced as a stop-gap. It has a half life twice as long as cobalt 60. Its effective energy is the same and it has many of the irradiation advantages of cobalt 60. It is probably not so satisfactory as cesium 137.

ENERGY

The energy levels and the kind of radiation desired by the therapist must be considered by the brachytherapy designer. Almost any energy up to 3.5 million volts for either beta or gamma radiation can be procured from the isotopes available. The choice, however, is not so great when one takes all the other factors into consideration. With the conventional radium isotope, a mixture of high- and low-energy gamma rays and a continuum from high- to low-energy beta rays was all that was available to the brachytherapist. With radioisotopes the choice is more flexible. For the few problems in which a pure beta emitter is desirable, the obvious choices have already been investigated. An yttrium isotope with a few days' half life and a high energy has been used. Since yttrium is not a normal constituent of the body, it is well tolerated

in even colloidal injections. The phosphorus isotope has a few weeks' half life. It has a high energy, it is easily procurable, and its chemistry is well known. But phosphorus is a normal metabolite of the body and it is difficult to control its deposition if the carrying vehicle comes in contact with body tissues. There are few very low-energy and a few very long half life pure beta emitters, carbon 14 and sulfur 35, for example. Pure beta emitting gases and liquids are easily available possibilities. However, all of these are attended with problems that have not yet been satisfactorily solved.

Within the list of gamma emitters those that give off rays of energies much greater than one million volts will result in total body irradiation. This is not, strictly speaking, brachytherapy. In the one million volt range there are many choices; cobalt 60 and europium 152 appear to be the most practical. In the half million volt range the cesium and cerium isotopes are ideal. They are plentiful but their practical use depends upon problems of loading and handling. Very few isotopes in the few hundred kilovolt range appear to be satisfactory from the standpoint of such considerations as half life, contamination, protection, and so on. A brachytherapist can find many very practical solutions to his problems if he can use an isotope giving off an emission of less than 100 kilovolts.

EXAMPLES OF POINT SOURCES AND EXTENDED SOURCES

Almost all the suggestions made before 1910 (using radium as the source of activity) have now been either duplicated or improved upon with artificially produced radioactive isotopes. The use of cobalt 60, or the slightly better europium 152, in the familiar Ernst-type applicators, or Heyman-type applicators, is illustrated in Figure 1. The problem to be solved in the Bowman Gray applicator was to make one that was easily inserted without excessive exposure to the loader, operator, or manufacturer. This device solved some of the problems of protection, solved all the problems of contamination, but it has some disadvantage over radium in having only a 12½ year half life. There is less electron contamination. There is no possibility of

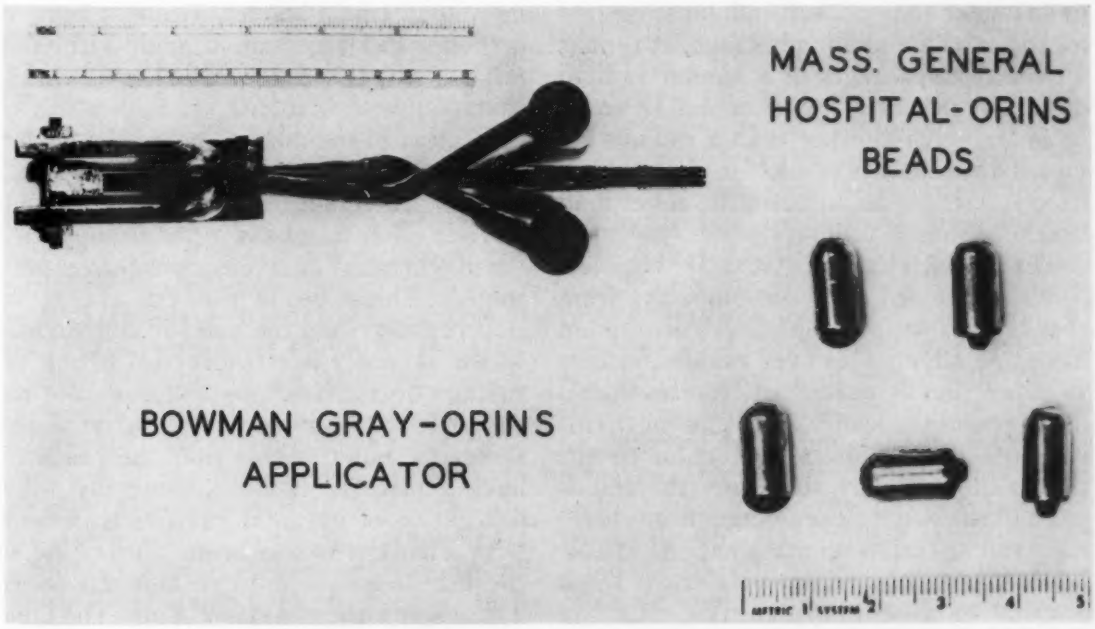

Fig. 1. The Bowman Gray applicator and MGH-ORINS beads; brachytherapy devices using europium 152.

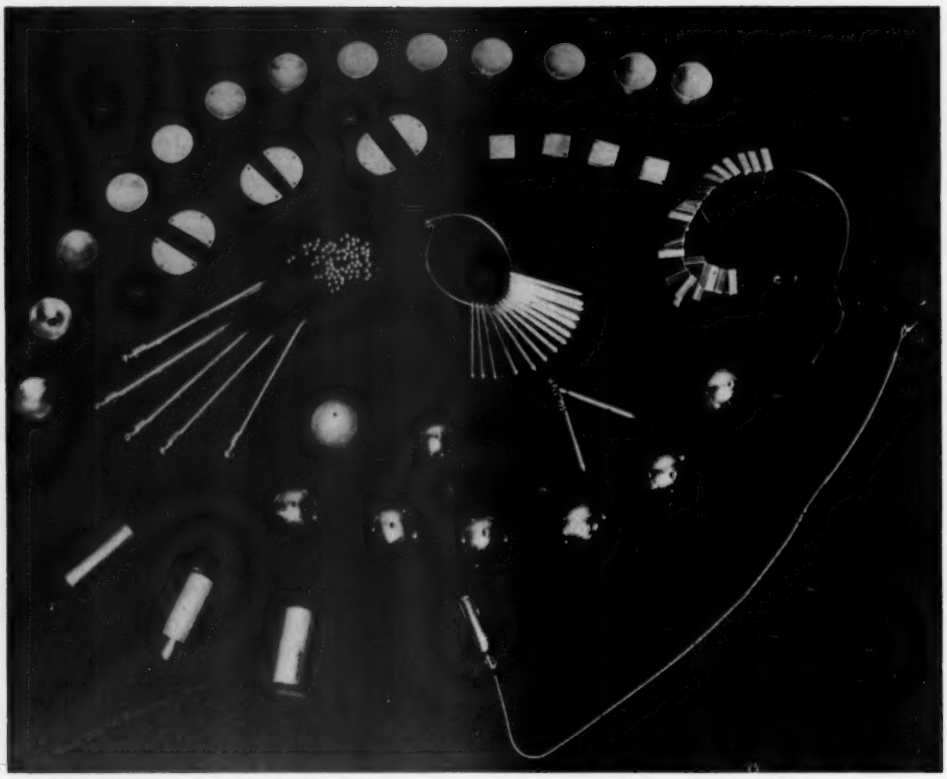

Fig. 2. Cobalt 60 applicators made from Incoray alloy (International Nickel Company).

chemical contamination. The energy is a little higher than that of radium since it is mostly in the million volt range. It retains all the disadvantages of a similar radium device in practice, but it probably could be made much cheaper than a radium device. The dosimetry of such an applicator is fixed and its use might be a little easier than that of a similar radium device.

The Massachusetts General Hospital beads are copied with europium 152 from the Heyman-type applicator. Europium has some advantages over radium, insofar as protection is concerned, to the manufacturer and the loader. It has all the disadvantages of radium in protection to the therapist. It is very safe from the standpoint of the patient's protection from chemical and electron contamination. These beads could be inexpensive devices for a hospital to possess in quantity.

In Figure 2 is shown one of the first applications of the Incoray alloy beads. The beads have been made in sizes from 1 mm. to 2 cm. diameter. Beads 5 mm. in diameter and larger can be made with more millicuries of activity than any brachytherapist wishes to use. The problems of protection to the manufacturer, the loader, and to the patients are solved. The problems of protection to the therapist are not solved. The problems of contamination (both chemical and electron) have been solved. These beads use the cobalt 60 isotope; therefore, the half life is five years which is really too short for a brachytherapy device. They are obviously not the complete answer to all brachytherapy problems, but it seems that the beads do have a place in therapy, especially when irradiation of irregular cavities is desired.

In Figure 3 is shown an illustration of the use of gold 198 (or cobalt 60) seeds. These seeds are in nylon tubing. The Ohio State University group has gone to considerable time and trouble to produce a

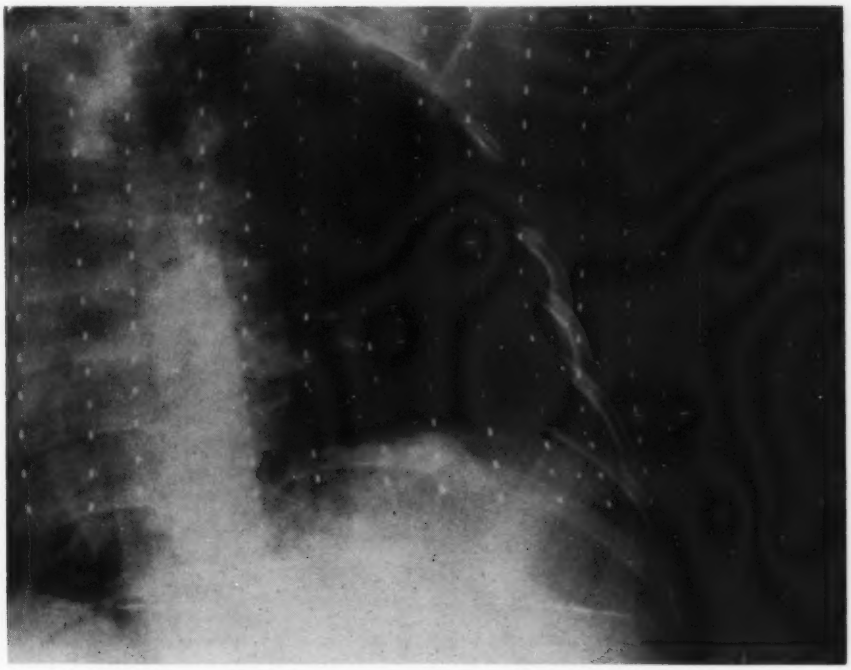

FIG. 3. Gamma-ray seeds in nylon thread, Ohio State University.

feasible solution to some brachytherapy problems on a practical level of clinical therapy. The protection problems are not solved for the manufacturer or the loader. They are partially solved for the therapist and are probably completely solved for the patient. There is no chemical or electron contamination with this kind of device. The half life of these isotopes is short but the method of preparing nylon encapsulated point sources has been solved by the Ohio State group. The energy levels and the half lives of these devices can be adjusted by selection of isotopes to suit the desires of the therapist.

An extension of the idea of using hollow tubing is illustrated in Figure 4. The University of Chicago group has worked out a method in which the surgeon sews a hollow tubing into place surrounding a tumor. The two ends of this tubing come out through the surgical wound. Mercury is injected into the tubing and with roentgenographic techniques the positioning of the hollow tubing is ascertained. The mercury is then taken out and a radioactive isotope is injected into the tubing. This can be washed out at any time. With this idea there is practically no protection problem to the manufacturer, the loader, the therapist, nor need there be a protection problem to the patient. There is only a small possibility of chemical contamination. The electron contamination depends upon the isotope used. Problems of half life and energy are almost completely at the discretion of the therapist, and his control over dosage is as good or better than in any other brachytherapy usage. This method of approaching the brachytherapy problem is probably as close to the ideal as is possible.

In Figure 5 are shown some of the isodose curves measured by Becker and Scheer of Heidelberg. In this particular example Becker and Scheer have mixed some cobalt 60 isotope into a modeling clay. Great flexibility of design and dosage control was achieved, but at the expense of protection and contamination. The idea is not limited to cobalt 60; many other isotopes that could effectively solve these problems could be used. A number of Incoray alloy metallic disks have been manufactured to match the kind of flexibility that Becker

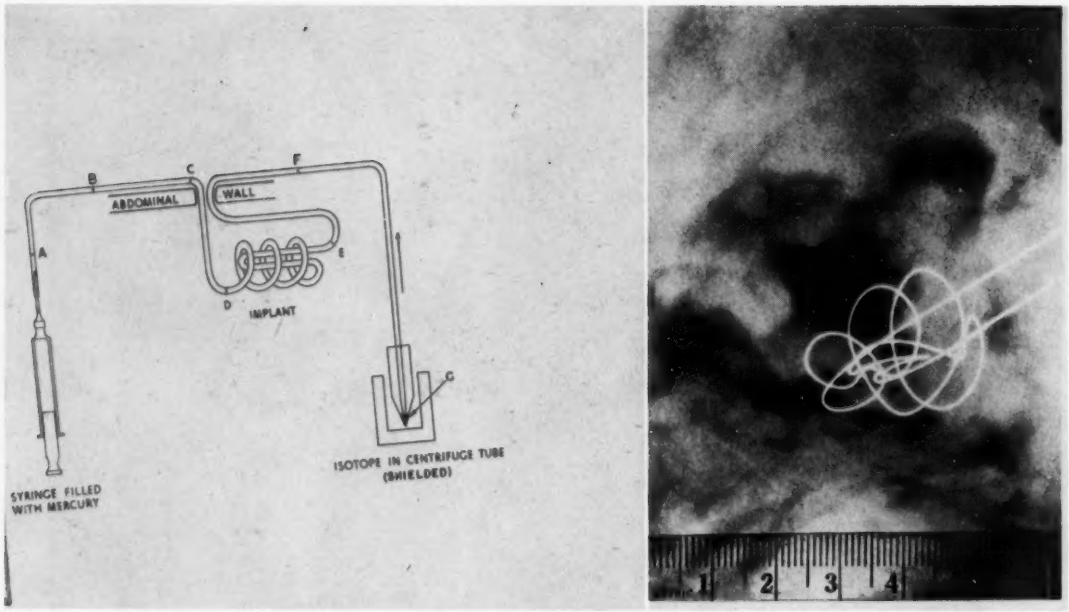

Fig. 4. Gamma-ray emitters in nylon tubing, University of Chicago.

and Scheer achieved with the modeling clay. Flexibility of application was sacrificed for a partial solution to the protection and contamination problems. Both systems have compensating advantages and disadvantages.

In Figure 6 is shown another attempt by the University of Chicago. The design was to manufacture a ceramic pellet containing a relatively short-lived beta emitter. The problems of protection are minor in this example. The problems of contamination

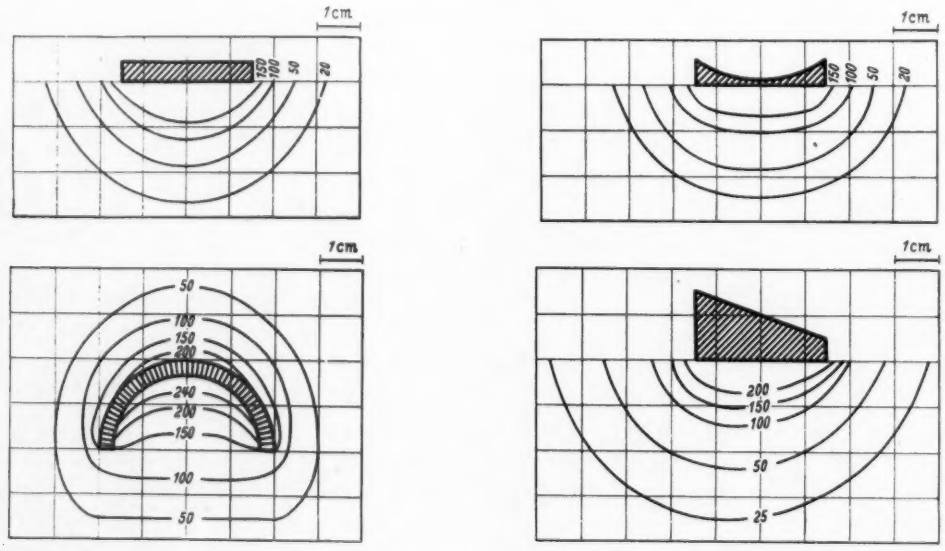

Fig. 5. Four of many isodose patterns possible with the Becker and Scheer (Heidelberg) modeling clay. Upper left: Isodose curve of a disk 3 cm. in diameter and .5 cm. in thickness. Upper right: Isodose curve of a concave disk 3 cm. in diameter. Lower left: Isodose curve of a cap with a 3 cm. radius. Lower right: Isodose curve of a wedge-shaped disk 3 cm. in diameter and increasing from .5 to 1.5 cm. in thickness. (Reproduced by permission from *Strahlentherapie*.)

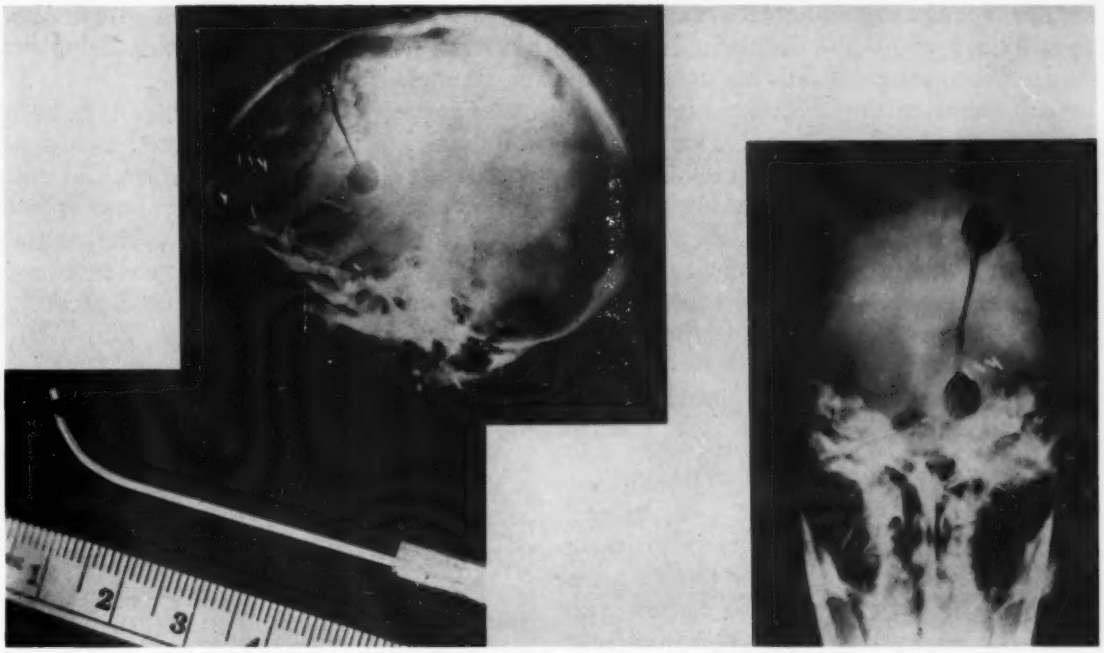

Fig. 6. Beta-ray emitter in ceramic pellets developed at the University of Chicago for surgical implantation.

are also minor since a short-lived isotope is used and the intention was to employ beta rays in cases where specific localization is both desirable and practical. This is probably close to an ideal answer to this clinical problem.

One of the very common suggestions even before 1910 was the request by surgeons for a paint, or a liquid, or some kind of radium device that could be applied to the edges of tumors after surgery. Many of these ideas were tried but never with outstanding success. In Figure 7 is shown one attempt by a surgeon to position a gelfoam

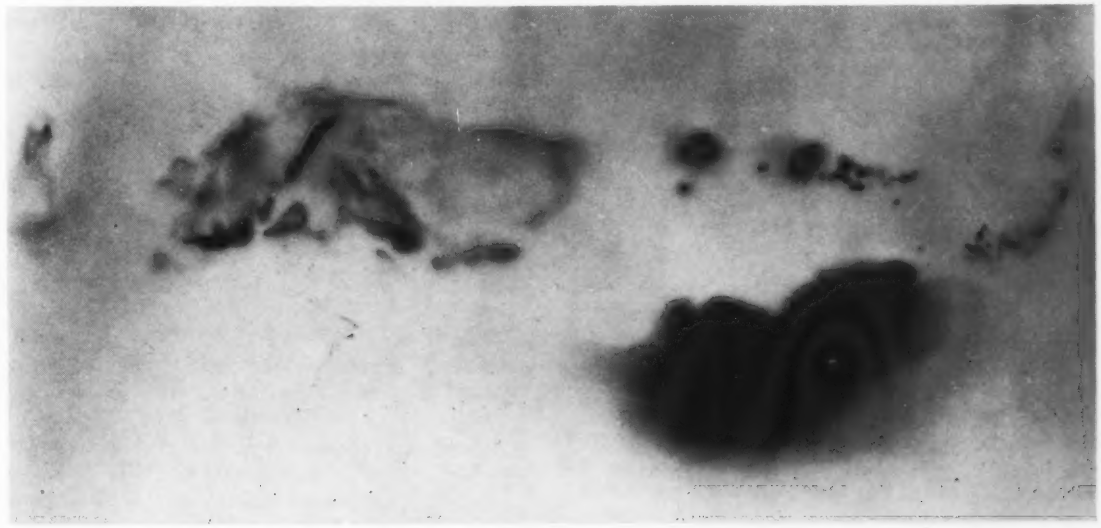

Fig. 7. Autoradiogram of the mediastinum of a dog after sham operation for bronchogenic carcinoma. The dark splotch on the lower right is from lutecium 177 in an implanted gelfoam sponge.

surgical sponge impregnated with lutecium 177. The sponge was implanted by the surgeon into the mediastinum of a dog after an operation that simulated lobectomy for carcinoma of the lung. The mediastinum was removed after a week and was compressed flat for an autoradiogram. The result is shown in Figure 7. Most of the lutecium has stayed in the surgical sponge but it has been picked up by the surrounding lymph nodes. The idea of lymph-node pick-up is intriguing and it deserves more thought and experiment by brachytherapists in the future.

THE OAK RIDGE MEDICAL DIVISION PROGRAM

In the Oak Ridge Institute of Nuclear Studies, Medical Division, we do not have the kinds of patients nor the therapeutic staff to do research on brachytherapy along clinical lines. However, since this is an important part of the dosimetry program of the Medical Division, a limited number of design ideas are being attempted. The clinical follow-up of these ideas is being done by about 20 radiotherapists who are interested in brachytherapy. No attempt has been made to develop a full brachytherapy program but rather we have concentrated on ideas that are not being investigated elsewhere.

A number of guiding principles have been followed. First we have adopted as a generalization that any brachytherapy idea that is not clinically superior to radium is not worth investigating. Second, the initial cost and all other economic considerations of an isotope idea must at least match the cost of using radium devices. Third, the protection and contamination problems are important and we must think not only of the therapist but also of the radiation protection of the manufacturer, the loader, and the patient. The history of brachytherapy is a long and distinguished one. For all practical purposes it is the radium problem. Radium thus becomes the unit of comparison for any brachytherapy idea. If a brachytherapy idea appears to achieve something better than can be done with radium, then the idea is probably worth investigating.

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Director of Instructional Courses: H. O. Peterson, St. Paul, Minn., *Manager of Annual Meeting:* James C. Cook, 110 Professional Building, Detroit 1, Mich.

Editor: Lawrence Reynolds, 110 Professional Building, Detroit 1, Mich.

Fifty-ninth Annual Meeting: Shoreham Hotel, Washington, D. C., September 30–October 3, 1958.

AMERICAN RADIUM SOCIETY

President: Milford D. Schulz, Boston, Mass.; *President-Elect:* Theodore R. Miller, New York, N. Y.; *1st Vice-President:* Theodore P. Eberhard, Ann Arbor, Mich.; *2nd Vice-President:* James F. Nolan, Los Angeles, Calif.; *Secretary:* Robert L. Brown, P. O. Box 459, Emory University, Ga.; *Treasurer:* Jesshill Love, 234 Medical Arts Bldg., 1169 Eastern Parkway, Louisville, Ky.

Executive Committee: Grant H. Beckstrand, Chairman, Long Beach, Calif.; Norman A. McCormick, Windsor, Ontario, Canada; Ralph T. Ogden, Hartford, Conn.

Program Committee: Milford D. Schulz, Chairman, Boston, Mass.; Lloyd F. Craver, New York, N. Y.; Morton M. Kligerman, New York, N. Y.; Elizabeth F. Focht, New York, N. Y.; J. Samuel Binkley, Oklahoma City, Okla.; Justin J. Stein, Los Angeles, Calif.; William S. MacComb, Houston, Texas; Theodore R. Miller (ex officio), New York, N. Y.

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Janeway Lecture Committee: Gioacchino Failla, Chairman, New York, N. Y.; H. Dabney Kerr, St. Michaels, Md.; Lloyd F. Craver, New York, N. Y.

Representatives on the American Board of Radiology: Douglas Quick, New York, N. Y.; B. P. Widmann, Philadelphia, Pa.; Frederick W. O'Brien, Boston, Mass.

Representatives on National Committee on Radiation Protection: Edith H. Quimby, New York, N. Y.; Theodore P. Eberhard, Ann Arbor, Mich.

Representative on the Board of Chancellors of the American College of Radiology: Charles L. Martin, Dallas, Texas.

Committee on Arrangements: Charles C. Stetson, Chairman, Englewood, N. J.; Henri LeClaire, Cincinnati, Ohio; Victor A. Marcial, Puerto Rico; Howard H. Ashbury, Charlottesville, Va.; Jesshill Love, Louisville, Ky.

Forty-first Annual Meeting: The Homestead, Hot Springs, Virginia, April 6–8, 1959.

EDITORIAL

THE FORTIETH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE American Radium Society held its Fortieth Annual Meeting in Hollywood, Florida on March 27, 28 and 29, 1958 at the Hollywood Beach Hotel. The attendance was greater than that of the previous year. The total registration was 484 which included 129 members, 197 nonmembers and 158 wives.

The meeting was called to order Thursday morning by Dr. Ralph T. Ogden of Hartford, Connecticut who delivered the Presidential Address. His philosophy was motivated by a conviction that the results from radiation treatment of cancer were not always as good as they should be, and that they would be improved if patients with cancer always received the best irradiation had to offer. Patients with cancer expect the best treatment available and when the modality chosen is irradiation, it is the radiologist's responsibility to see that they receive the best in his field, even if it requires referral to another center which has the proper facilities. This field is a large one because radiation therapy in the hands of the well trained and experienced physician stands equal to any other procedure as a primary treatment for cancer, and it plays a major role in the treatment of incurable, recurrent, and terminal phases of malignant diseases as well. All told, many cancers are treated by irradiation and, thus, it is doubtful if anyone plays a greater part than the radiologist in the over-all management of the patient with cancer unless it be the general practitioner.

The morning program continued with a presentation of a paper by Dr. Manuel Lederman of the Royal Marsden Hospital of London on his twenty-five years of experience with radiation therapy of malignant tumors of the nasopharynx. The next two communications were devoted to treatment of the tongue by surgery, radiation therapy and combination techniques. Dr. Gilbert H. Fletcher and his group from the M. D. Anderson Hospital in Houston, Texas, presented an interesting comparison of medium voltage and supervoltage roentgen therapy in the treatment of oropharynx cancers. They showed that 2 mev. and cobalt 60 unit equipment provides a means of delivering high tumor doses to lesions involving the retromolar trigone, anterior faucial pillars, soft palate, glossopalatine sulcus, base of tongue, valleculae and pharyngeal walls and possibly to metastatic lymph nodes. The last two papers of this session pertained to the use of interstitial radium therapy about the head and neck. Dr. Oscar L. Morphis of Fort Worth, Texas, discussed his ingenious method of using teflon tubes with radium sources in order to afford adequate protection to both operator and technician.

At the second scientific session in the afternoon, Dr. Lloyd F. Craver of New York City acted as moderator of a Symposium and Round Table Conference on Chemotherapy in the Treatment of Cancer. Each of the six speakers presented his material in a well organized manner. The subjects included treatment of acute leukemia, malignant lymphomas and solid tumors, the prophylactic use of alkylating agents in surgery for cancer, studies of quinoline and acridine derivatives of nitrogen mustard for the chemotherapy of multiple myeloma and malignant lymphomas and chemotherapy from the pathologist's point of view. Many

questions were asked from the audience, as well as by the members of the panel, and an excellent discussion followed. While this session was in progress, the wives and children of the members and guests were entertained by a sightseeing and shopping tour in Miami Beach.

In the early evening, a reception sponsored by the Radium Chemical Company was held in the beautiful Hotel Gardens. Owing to the pleasant weather, beautiful surroundings and the congeniality of those in attendance, this Social Hour was thoroughly enjoyed by the members and guests of the American Radium Society. Following an informal dinner in the Mayfair Room, Dr. Gioacchino Failla, in his introductory address, recounted in some detail biographical events in the career of Dr. Leonidas D. Marinelli, this year's Janeway Lecturer. Dr. Marinelli spoke on *Natural Radioactivity in the Human*, referring particularly to radium content in the skeleton as obtained from drinking water, dial painting, diagnostic thorotrast injection and from other sources. With the advent of fall-out from nuclear detonation, the subject has gained considerably greater attention. Although much information has been obtained from work on experimental animals, the evaluation of bone cancerogenesis in man due to natural radioelements can only be accomplished by cooperative effort throughout the world by (1) follow-up of dial painters who worked in the early decades of this century, (2) observations of patients who have been injected with thorotrast for diagnostic purposes and who are estimated to have from 0.5 to 2.0 maximal permissible burdens of mesothorium in their bones, (3) observations on "high level" groups here and abroad who live in localities where potable waters are relatively richer in radium, and (4) observations on populations living in areas where external background radiation is high, such as in India and Brazil. Dr. Marinelli presented interesting figures on his own work involving about 300,000 people in one-half of the counties of Illinois, where drinking water has a relatively high radium content. He concluded his lecture by recommending that others here and abroad initiate studies of this sort, by calling for a cessation of sterile squabbling on the subject and for a concerted effort to obtain objective evidence.

At the third scientific session, during the morning of the second day, a variety of subjects were discussed, including the metabolic behavior and clinical response of radioactive iodinated rose bengal in patients with inoperable cancer of the biliary system, radiation and leukemia in relation to the liver, primary lymphosarcoma of the stomach, transverse laminagraphy and its application to radiation therapy, high pressure oxygen and roentgen therapy, the modification of the radiation response and management of the late breast cancer.

The fourth scientific session in the afternoon was a Round Table Conference on Carcinoma of the Cervix moderated by Dr. A. N. Arneson of St. Louis, Missouri. The five members of the panel spoke on the time-dose relationships in the treatment of Stage I lesions, the use of interstitial paracervical and parametrial radium needles, the use of radiogold, the value of radical surgery, and the optimal radiation dosage in cancer of the cervix. These subjects were presented concisely with supporting statistics and many questions were asked by members of the audience. An enthusiastic discussion was entered into by the panel members. During this session, the ladies were entertained by a Jungle Cruise through the waterways of Fort Lauderdale and through the Everglades. This was a trip well to be remembered for its fascination and interest.

On the evening of the second day a Social Hour was followed by the Annual Banquet. Dr. Ralph T. Ogden graciously presented the Janeway Medal to Dr. Leonidas D. Marinelli and commended him for the excellence of his scientific contributions as exemplified in his Janeway Lecture.

The fifth and last scientific session was held on Saturday morning and included

several contributions on cobalt 60 teletherapy. The subjects comprised the physical factors, clinical considerations and limitations of Co^{60} therapy, a precision Co^{60} unit for fixed field and rotation therapy and the delusion of depth dose in Co^{60} treatment of cancer. Two other papers were presented, one on radioactive chromium gamma ray sources and the other on the treatment of pterygium by surgery followed by Sr^{90} beta radiation.

At the final executive session of the society, President Ogden expressed his sincere appreciation for the work done by the various committees and especially to the members and wives of the Committee on Arrangements.

All in all, the meeting was unusually successful from the standpoint of attendance, scientific presentation and social events.

HARRY HAUSER, M.D.

SOCIETY PROCEEDINGS AND NEWS ITEMS

PROGRAM OF THE TWENTIETH MIDSUMMER RADIOLOGICAL CONFERENCE OF THE ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

SHIRLEY-SAVOY HOTEL, DENVER, COLORADO

AUGUST 14, 15 AND 16, 1958

Thursday Morning, August 14

9:00–10:45 A.M.
Registration

10:45–11:30 A.M.
Addresses of Welcome:
Rocky Mountain Radiological Society
Angus K. Wilson, M.D., Salt Lake City, Utah, President
The Radiological Society of North America
Leo G. Rigler, M.D., Los Angeles, California, President
The American Roentgen Ray Society
Wendell G. Scott, M.D., St. Louis, Missouri, President
The American College of Radiology
Vincent W. Archer, M.D., Charlottesville, Virginia, President
Colorado Radiological Society
James W. Lewis, M.D., Colorado Springs, Colorado, President
Colorado State Medical Society
Clare C. Wiley, M.D., Longmont, Colorado, President
Denver Medical Society
James M. Perkins, M.D., Denver, Colorado, President

(30 min.) 11:30–12:00 NOON
Radiation Hazards.
Leo G. Rigler, M.D., Los Angeles, California

12:00–1:15 P.M.
Luncheon—Informal Meeting with Guest Speakers
Angus K. Wilson, M.D., President, Rocky Mountain Radiological Society, Presiding

Thursday Afternoon, August 14

(30 min.) 1:15–1:45 P.M.
The Amplifying Fluoroscope Screen
B. Kazan, RCA Laboratories, Princeton, N. J.

(20 min.) 1:45–2:05 P.M.
The Amplifying Fluoroscope Screen—Its Present Uses and Limitations
Ellwood W. Godfrey, M.D., Princeton, N. J.

(15 min.) 2:05–2:20 P.M.
Question and Answer Period—
Mr. Kazan and Dr. Godfrey, Presiding

(20 min.) 2:20–2:40 P.M.
Doxinate as an Adjunct in the Roentgenological Investigation of the Digestive Tract
Angus K. Wilson, M.D., Salt Lake City, Utah

(30 min.) 2:40–3:10 P.M.
Destructive Changes in Bone
Gwilym S. Lodwick, M.D., Columbia, Missouri

3:10–3:50 P.M.
Visit the Exhibits

(30 min.) 3:50–4:20 P.M.
Mr. Robert Morrison, Eastman Kodak Company, Rochester, N. Y.

(40 min.) 4:20–5:00 P.M.
Estimation of the Duration of Human Cancer Prior to Diagnosis
Vincent P. Collins, M.D., Houston, Texas

5:00 P.M.
Executive Session

Thursday Evening, August 14

6:00 P.M.
Guest Speakers' Dinner—Informal. All Members, Visiting Radiologists and Wives Invited
Shirley-Savoy Hotel

8:00 P.M.
Memorial Lecture in Honor of Dr. James P. Kerby—Joint Meeting with the Denver Medical Society
A Review of the Clinical and Radiographic Features of Infantile Cortical Hyperostosis
John Caffey, M.D., New York, N. Y.

Friday Morning, August 15

(20 min.) 9:00–9:20 A.M.
Some Delayed Radiation Effects
Gerald S. Maresh, M.D., Denver, Colorado
(40 min.) 9:20–10:00 A.M.
Recent Advances in the Chemotherapeusis of Cancer
Henry D. Diamond, M.D., New York, N. Y.
(30 min.) 10:00–10:30 A.M.
E. Dale Trout, Ph.D., General Electric X-ray Company, Milwaukee, Wisconsin
10:30–11:00 A.M.
Visit the Exhibits
(20 min.) 11:00–11:20 A.M.
Beam Quality Studies. I. Human Cells in Vitro.
Arnold Feldman, M.S., Dimitry Morkovin, M.D., John. S. Bouslog, M.D., and Raymond R. Lanier, M.D., Denver, Colorado
(40 min.) 11:20–12:00 NOON
A Three-step Method for the Nonsurgical Identification of Solitary Pulmonary Nodules
L. Henry Garland, M.D., San Francisco, California
12:00–1:30 P.M.
Two separate luncheons with half of the guest speakers in each room

Friday Afternoon, August 15

(40 min.) 1:30–2:10 P.M.
The Well-balanced Foot: Variations and Anomalies
Ellwood W. Godfrey, M.D., Princeton, New Jersey
(40 min.) 2:10–2:50 P.M.
Estimation of the Effects of Cancer Treatment
Vincent P. Collins, M.D., Houston, Texas
(40 min.) 2:50–3:30 P.M.
Normal Variants in the Growing Skull; Their Significance in the Radiographic Diagnosis of Trauma
John Caffey, M.D., New York, N. Y.
3:30–3:40 P.M.
Visit the Exhibits
(40 min.) 3:40–4:20 P.M.
Experiences in the Clinical Radiotherapy of the Lymphomas
L. Henry Garland, M.D., San Francisco, California
(40 min.) 4:20–5:00 P.M.
Lymphosarcoma: A Total Experience at Memorial Center
Henry D. Diamond, M.D., New York, N. Y.
5:00 P.M.
Executive Session

Friday Evening, August 15

6:00 P.M.
Social Hour—Shirley-Savoy Hotel
7:00 P.M.
Banquet—Informal—Shirley-Savoy Hotel
Angus K. Wilson, M.D., President, Rocky Mountain Radiological Society, Presiding
The Shadow of Research
L. Henry Garland, M.D., San Francisco, California

Saturday Morning, August 16

(40 min.) 9:00–9:40 A.M.
Achondroplasia of the Growing Pelvis and Spine
John Caffey, M.D., New York, N. Y.
9:40–10:15 A.M.
Visit the Exhibits
10:15–12:15 P.M.
Roentgen Film Diagnoses
Panel Discussion
12:15 P.M.
Luncheon with the Guest Speakers

Saturday Evening, August 16

Trip to Central City
5:30 P.M.
Social Hour—Teller House
6:30 P.M.
Dinner at the Teller House, Central City, Colorado
8:15 P.M.
Play–Central City Opera House

NOTE: Anyone desiring a ride to Central City and anyone who can take extra passengers, please contact Mrs. Bemis at the Registration Desk as soon as possible.

FIRST ANNUAL SYMPOSIUM ON CINEFLUOROGRAPHY

Sponsored by The Department of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

Time:

Friday and Saturday, November 14 and 15, 1958 (just prior to the Annual Meeting of The Radiological Society of North America, which begins on Sunday, November 16).

Program:

First day: Cinefluorographic equipment and technique. Appraisal of image intensification apparatus, film emulsions and film sizes, processing, viewing and interpretation. Radiation dose problems.

Second day: Clinical application with detailed consideration of a major organ system.

Details of program and local arrangements will appear in the near future.

General Chairmen

Dr. George H. Ramsey
Dr. James S. Watson, Jr.

Program Chairman

Dr. Theodore A. Tristan

Local Arrangements

Dr. Lee B. Lusted

Please address all inquiries concerning the Symposium to:

Dr. George H. Ramsey
Department of Radiology
Strong Memorial Hospital
Rochester 20, N. Y.

DOCTOR EDWARD L. JENKINSON HONORED

Doctor Edward L. Jenkinson, Professor of Radiology and Chairman of the Department, Northwestern University School of Medicine, Chicago, Illinois, retired in May of this year after forty-one years as Director of the Department of Radiology of St. Luke's Hospital, Chicago.

Doctor Jenkinson is Past-President of the American Roentgen Ray Society and he has held throughout the years numerous offices of importance in the Society.

His retirement as Director of the Department of Radiology, St. Luke's Hospital, with which he has been so long intimately associated, will bring a great sense of regret to his many friends throughout the country.

As a token of the deep appreciation and high regard for Doctor Jenkinson's services, his former residents in the Department of Radiology at St. Luke's Hospital have established the Edward L. Jenkinson Fellowship in Radiology at Northwestern University School of Medicine. This is a splendid tribute to one of the outstanding leaders in Radiology in this country.

SECOND AUSTRALASIAN CONFERENCE ON RADIATION BIOLOGY

The Second Australasian Conference on Radiation Biology will be held at the Cancer Institute, Melbourne, Australia, from December 15–18, 1958. Guest speakers at the Conference will be Dr. L. H. Gray, Director of the British Empire Cancer Campaign, Radiobiological Research Unit, Mount Vernon Hospital, London, and Dr. J. F. Loutit, Director of the Medical Research Council Radiation Biology Unit, Harwell, Didcot, Berks, England. Proffered papers on relevant subjects are invited, and titles and a 250 word abstract should be in the hands of the Convener by July 31, 1958. Registration forms and other information for those wishing to attend may be obtained from the Convener, Dr. J. H. Martin, Physics Department, Cancer Institute Board, 483 Lt. Lonsdale Street, Melbourne, Victoria, Australia.

SEVENTH CONFERENCE ON HOT LABORATORIES AND EQUIPMENT

Abstracts for papers to be presented at the Seventh Conference on Hot Laboratories and Equipment to be held in Cleveland, Ohio, April, 1959, are due September 15, 1958 and should be sent to Program Chairman, L. G. Stang, Jr., Brookhaven National Laboratory, Upton, New York. Deadline for papers will be announced later. Papers are invited on all phases of hot laboratories and equipment for handling radioactive material including design, construction, operation, maintenance, decontamination, remodelling, shielding calculations, costs, etc.

THE SEVENTH ANNUAL IRA I. KAPLAN LECTURE

The Seventh Annual Ira I. Kaplan Lecture "Thirty-three Years' Experience in Small Dose Irradiation of 640 Women for Infertility" was presented by Dr. Ira I. Kaplan on May 8, 1958 at 5:30 P.M. at

Lore-Wertheim Room, Alumni Hall, N.Y.U., Bellevue Medical Center, 550 First Avenue, New York, New York. The lecture was discussed by Dr. Marshall Brucer.

AMERICAN RADIUM SOCIETY ELECTS NEW OFFICERS

At a meeting held in Hollywood, Florida, on March 27–29, 1958, the following officers were elected: President, Milford D. Schulz, Boston, Mass.; President-Elect, Theodore R. Miller, New York, N. Y.; 1st Vice-President, Theodore P. Eberhard, Ann Arbor, Mich.; 2nd Vice-President, James F. Nolan, Los Angeles, Calif.; Secretary, Robert L. Brown, P.O. Box 459, Emory University, Ga.; and Treasurer, Jesshill Love, 243 Medical Arts Building, Louisville, Kentucky.

We regret to announce the sudden death on April 10, 1958 of Dr. William W. Bryan of Atlanta, Georgia, distinguished member of the American Roentgen Ray Society.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

PROGRESS IN GYNECOLOGY. Volume III. Edited by Joe V. Meigs, M.D., Clinical Professor of Gynecology, Harvard Medical School; and Somers H. Sturgis, M.D., Clinical Professor of Gynecology, Harvard Medical School. Cloth. Price, $15.50. Pp. 780, with numerous illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, New York, 1957.

Like its predecessors, the Third Edition of Progress in Gynecology presents an extensive compilation of current concepts in the field of gynecology. This task was admirably accomplished by the Editors and the 69 contributors, American and foreign, all experts in their separate fields. Together they have produced a total of 55 separate articles dealing with (1) Growth and Physiology (2) Diagnostic Methods (3) Functional Disorders (4) Inter-Relationships of Endocrine Glands (5) Sterility and Reproduction (6) Infections (7) Benign Growths (8) Malignant Growths (9) Operative Technics and (10) Preoperative and Postoperative Care.

The gynecologist can read every one of the 755 pages of text with profit.

For the radiologic readers of THE JOURNAL there are many chapters which should help them understand better the gynecologist's viewpoint in their common problems. Among the topics which might be singled out for special reading by radiologists are: Damage to Offspring of Irradiated Women by Irwin H. Herskowitz; Adenocarcinoma of the Endometrium by John McKelvey and K. A. Prem; Preoperative Radium Irradiation in the Treatment of Cancer of the Cervix by John Burch, Robert Chalfant and Horace Lavely, Jr.; Radiotherapy in the Treatment of Cancer of the Uterine Cervix by Milford Schulz and John Graham; Radiation Therapy and Excision of the Lymph Nodes in Cervical Cancer by Gunnar Gorton; Radioactive Colloidal Gold in the Treatment of Cancer of the Cervix and Cancer of the Ovary by Alfred Sherman and Willard Allen; Use of Cobalt 60 in Radiation Therapy of Gynecologic Malignancies by Allen Barnes.

For ready access to current gynecologic thought on such items of common interest and as a reference book to up-to-date thinking in other fields of gynecology, this book can be strongly recommended. It includes in one volume a mass of informative material which could not be assembled without access to a multitude of special journals and texts.

HAROLD C. MACK, M.D.

RÖNTGENDIAGNOSTIK DES LUMBALEN BANDSCHEIBENRISSES UND SEINER FOLGEN. Radiologia Clinica. Supplement to Volume 26. By H. H. Weber. Paper. Pp. 72, with 60 illustrations and 5 tables. S. Karger, Basel, Switzerland, 1957.

Herniation of the intervertebral disk is regarded as the final stage of a degenerative process, which often begins in infancy, *i.e.*, after cessation of blood supply precludes the possibility of regeneration of the meniscus. Nutritional disturbances (bradytrophy) lead to loss of elasticity, and thus to excessive susceptibility to small and repeated trauma. As a part of the wear and tear of osteochondrosis, the herniated disk may cause spurring and lipping, which is reactive bone deposited after damage of the vertebral cortex by the protruding meniscus.

The disk may rupture without disturbing the width of the intervertebral space, a fact repeatedly shown by histologic correlation of autopsy material with previous roentgenograms. Narrowing, however, always indicates some damage of the disk, even if it can be demonstrated at times only in the erect position, and not in recumbency. Clinical findings (inspection, palpation, neurologic changes) are never sufficient for a positive diagnosis of herniated disk, because similar symptomatology may be induced by spondylitis, vertebral tumor, or radicular neurinomata. In the author's hands, myelography (not to speak of the even more specific diskography) revealed excellent diagnostic efficacy, being confirmed, both to location and side, in each and everyone of the 54 operated cases of lumbar disk herniation (25 at L4/L5 and 26 at L5/S1), summarized in the text. On conventional roentgenograms, the earliest sign was posterior dislocation of the adjacent ver-

tebral body, which is not due to herniation itself, but to rupture of the posterior aspect of the disk. Interposed soft tissues in most cases block the possibility of anatomic restoration, and then this condition (akin to the chiropractor's "subluxation") will be seen roentgenographically either in upright or recumbent position. This finding persists even after surgical correction of the prolapsed disk. In the reported series, posterior dislocation was more frequently encountered than narrowed intervertebral spacing.

Other statements, just as refreshingly unusual as the frequency of posterior dislocation, are included in this interesting monograph, well documented with stringent logic, satisfactory reproductions, and convincing pencil drawings. Even if the reader should disagree with some of the dogmatic opinions of the author (a well-known radiologist, who published early kymographic studies of diaphragmatic motion), he will find in this book a stimulating discussion of a problem which is not only common, but often perplexing, in everyday practice.

E. R. N. Grigg, M.D.

L'Arthrographie opaque du Genou. By Paul Ficat, Assistant de Chirurgie des Hôpitaux, Diplômé d'Électroradiologie. Cloth. Price, 3,800 fr. Pp. 244, with 139 illustrations. Masson et Cie, Éditeurs, 120 boulevard Saint-Germain, Paris 6e, France, 1957.

The author presents an excellent account of the diagnostic possibilities and limitations of the opaque arthrography of the knee joint. His work is the result of a study of 600 cases, all with surgical correlation and examined according to the technique of opaque arthrography established by Lindblom in 1948.

The author prefers opaque to gaseous material, the former being not compressible and readily miscible with the articular fluid, requiring no antiphysiologic positions, giving excellent contrast and enabling visualization of the chondromeniscal structures of the articular interspace. According to the author, gaseous arthrography is a good diagnostic method in skillful hands, but its explorative possibilities are more limited.

After a brief historic survey and anatomic review, the author describes the technique for opaque arthrography and discusses normal and pathologic arthrography according to his diagnostic criteria. He deals not only with the traumatic aspects of the menisci, but also with the congenital malformations, the degenerative changes of the joint cartilage and menisci and the synovial and capsuloligamentous lesions of the knee. All these subjects are exemplified by numerous roentgenographic reproductions and further illustrated with sketches.

The work is excellent and the iconography demonstrative. The book is highly recommended to radiologists and orthopedists having to deal with knee joint problems.

H. P. Levesque, M.D.

BOOKS RECEIVED

Tuberculosis in White and Negro Children. Volume I: The Roentgenologic Aspects of the Harriet Lane Study. By Janet B. Hardy, M.D.C.M. Cloth. Price, $7.50. Pp. 119, with numerous illustrations. Published for the Commonwealth Fund by the Harvard University Press, Cambridge, Massachusetts, 1958.

Tuberculosis in White and Negro Children. Volume II: The Epidemiologic Aspects of the Harriet Lane Study. By Miriam E. Brailey, M.D., Dr.P.H. Cloth. Price, $4.50. Pp. 103, with numerous tables. Published for The Commonwealth Fund by the Harvard University Press, Cambridge, Massachusetts, 1958.

Dr. W. C. Röntgen. By Otto Glasser, Ph.D., F.A.C.R. (Assoc.), Holder of Röntgen-Honor-Plaque of the Röntgen-Museum in Remscheid-Lennep, 1951; Professor of Biophysics, Frank E. Bunts Educational Institute; Head, Department of Biophysics, Cleveland Clinic Foundation, Cleveland, Ohio. Second edition. Cloth. Price, $4.50. Pp. 196, with 26 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1958.

Roentgenology of the Chest. Edited by Coleman B. Rabin, M.D., F.C.C.P., Attending Physician and Associate Radiologist for Chest Diseases, The Mount Sinai Hospital, New York City; Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. Cloth. Price, $19.50. Pp. 504, with 247 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1958.

Television in Science and Industry. By V. K. Zworykin, E. E., Ph.D., D.Sc.(hon.), Honorary Vice-President and Technical Consultant, Radio Corporation of America; E. G. Ramberg, Ph.D., Research Physicist, RCA Laboratories, Princeton, N. J.; and L. E. Flory, B.S. (E.E.), Research Engineer, RCA Laboratories, Princeton, N. J. Cloth. Price, $10.00. Pp. 300, with numerous illustrations. John Wiley & Sons, Inc., 440 Fourth Avenue, New York 16, New York, 1958.

Vol. 79, No. 6

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Head

Tönnis, W., Friedmann, G., and Albrecht, H. Zur röntgenologischen Differentialdiagnose der Hypophysenadenoma (Unter besonderer Berücksichtigung der primären und sekundären Sellaveränderungen). (The roentgenologic differential diagnosis of pituitary adenomas [with special consideration of the primary and secondary sella turcica changes]. *Fortschr. a. d. Geb. Röntgenstrahlen u. d. Nuklearmedizin*, Dec., 1957, *87*, 677–686. (From: Neurochirurgische Universitätsklinik Köln-Lindenburg and Max-Planck-Institut für Hirnforschung, Abteilung für Tumorforschung und experimentelle Pathologie, Köln-Lindenburg, Germany.)

From a study of 134 patients with pituitary tumors, 694 patients with various brain tumors, and 120 patients with tumors of the base of the skull, the authors conclude that no single sign or group of signs can be used to determine the histologic nature of a given lesion on the basis of roentgenographic findings alone. It is also often difficult to determine whether changes in the sella turcica are due to pituitary or extrasellar tumors. However, the latter may often be recognized by usual signs of space-occupying intracranial tumors: Separation of the sutures, increased digital impressions, displacement of the calcified pineal gland, and localized areas of bone destruction, hyperostosis, or calcifications within the tumor. Enlargement of the sella turcica occurred in 25 per cent of the cases associated with one or more of these findings in extrasellar tumors. Pressure atrophy of the sella turcica associated with extrasellar lesions is often striking and is characterized by decalcification rather than by thinning of the dorsum sellae. The dorsum sellae may also present a wedge-shaped shortening. The floor of the sella turcica is uniformly depressed. The anterior clinoid processes are rarely involved.

The most important change in pituitary tumors is the enlargement of the sella turcica. This occurred in 91.8 per cent of the cases compared to only 25 per cent enlargement secondary to extrasellar tumors. Using the measurements of Berghoff, less than 20 per cent of the pituitary tumors showed a Grade I enlargement, whereas 75 per cent of the cases of secondary sellar enlargement fell in the Grade I classification. Pituitary tumors as a rule cause a thinning of the dorsum sellae rather than decalcification. The contour also becomes sharper as a result. The tip of the dorsum sellae is often at the same level as the tuberculum sellae. With advanced destruction of the sella, its floor may reach the same depth as the middle cranial fossa. Even such extensive destruction does not mean a malignant process. A double contour of the sella turcica is found in 46.3 per cent of pituitary tumors in contradistinction to the smooth depression produced by extrasellar lesions. Decalcification or destruction of the anterior portion of the sella turcica is rare in secondary sellar enlargement but has been found in 23.9 per cent of primary sellar enlargement.—*J. Zausner, M.D.*

Tönnis, W., Friedmann, G., and Albrecht, H. Veränderungen der Sella turcica bei sellanahen Tumoren und Tumoren der Schädelbasis. (Alterations of the sella turcica in parasellar tumors and tumors at the base of the skull.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Dec., 1957, *87*, 686–692. (From: Neurochirurgische Universitätsklinik Köln-Lindenburg and Max-Planck-Institut für Hirnforschung, Abteilung für Tumorforschung und experimentelle Pathologie, Köln-Lindenburg, Germany.)

The diagnosis of an intracranial tumor can be made if all the direct and indirect signs are carefully observed. Such a diagnosis was made in 85 per cent of the 120 cases studied in this report. Osteoporosis of the sella turcica is not a reliable criterion in patients beyond forty-five years of age. Increase in the anteroposterior diameter of the sella is characteristic of tumors of the frontal lobe, whereas an increase in the depth of the sella occurs in occipital tumors. Localization of certain tumors may be made by the following considerations:

1. Olfactory meningiomas produce a localized hyperostosis or a destructive process in the anterior cranial fossa. One-third of the tumors in this series produced only changes in the sella turcica and could not be localized. Both the anteroposterior and vertical diameters were increased, so that they did not follow the general rule of anterior or frontal tumors.

2. Meningiomas of the sphenoid or middle fossa produced no characteristic changes in the sella turcica. The sphenoid tumors presented considerable hyperostosis locally, whereas middle fossa lesions caused marked destruction or showed calcification within the tumor. When middle fossa tumors enlarge posteriorly, they cause destruction of the petrous apex; if they grow anteriorly, they cause erosion of the lesser wing of the sphenoid, enlargement of the superior orbital fissure, and obscure the ethmoid cells. No typical changes were noted in the anterior clinoid processes or anterior wall of the sella.

3. Suprasellar tumors (meningiomas arising from the tuberculum sellae, epidermoids, and cholesteatomas) cause an anterior and downward displacement of the tuberculum sellae and a flattening of the anterior wall of the sella.

4. Parasellar chondromas and chordomas of the

clivus produce no characteristic changes in the sella turcica.

5. Unclassified tumors of the cranial base produce localized areas of destruction and a "pressure sella."

The most frequent finding, decalcification of the dorsum sellae, occurred in 68 per cent of the cases. Of these, only 26 per cent showed sellar enlargement, particularly the olfactory and suprasellar meningiomas. Findings limited to the sella turcica occurred in 31 per cent of all the cases, but in 72.5 per cent of suprasellar tumors. A double contour of the sella turcica is not considered a reliable sign of sellar involvement.—*J. Zausner, M.D.*

Haas, Lewis L. The posterior condylar fossa, foramen and canal, and the jugular foramen. *Radiology*, Oct., 1957, *69*, 546–552. (Address: Department of Radiology, University of Illinois, College of Medicine, Chicago 12, Ill.)

Normal variations in the posterior condyloid fossa and the jugular foramen may result in diagnostic difficulties. The condyloid fossa is best visualized in the occipital oblique and posteroanterior nuchofrontal projections, showing the posterior half of the foramen magnum. The fossa is visible adjacent to the posterior circumference of the foramen magnum, and is extremely variable in size and shape. The jugular foramen is visualized best in incomplete axial views and likewise may show variations in size, shape and detail. It is easily recognized at the posterior end of the petro-occipital fissure, lateral and anterior to the condyloid fossa. Both the jugular foramen and the condyloid fossa may be the sites of glomus tumor formation or metastatic carcinoma dissemination.—*Edward B. Best, M.D.*

Keim, H. Beitrag zur diagnostischen Verwertung von Abstandsdifferenzen zwischen dem Atlas und dem Dens Epistrophei im Röntgenbild. (Diagnostic evaluation of the difference in distance between the atlas and dens epistrophei on the roentgen film.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1957, *87*, 488–495. (Address: H. Keim, Institut für Physikalische Therapie und Röntgenologie der Univ. München, Ziemssenstr. 1, München 15, Germany.)

A very frequent diagnosis is the "subluxation in the atlanto-epistropheal joint" when the distance between the odontoid process of the axis and one of the lateral masses of the atlas is asymmetric. There is no doubt that an asymmetric position of the atlas may signify a pathologic finding. In many cases, the patient is asymptomatic. For the finding to be considered as a subluxation, the asymmetry must be constant regardless of the position of the patient. Except for errors in projection, asymmetric position of the atlas occurs quite frequently.

The following may produce asymmetric position: (1) Rotation in the region of the atlas-axis joint which can reach 30 degrees to each side; (2) rotation of the head and neck produces asymmetric projection of the entire epistropheus; (3) sideways bending or rotation of the head; and (4) variation in structure of the first 2 cervical vertebrae.

Studies were made on 25 young healthy individuals by taking sagittal roentgenograms of the atlas-axis portion of the cervical spine, in the mid-line and during active maximum right and left bending of the head. In 18 of the patients, there was a normal symmetric position of the atlas. In 6 of the other 7 cases where asymmetry was noted, a definite motion in the atlas-axis joint could be demonstrated, thus proving that the previously shown asymmetry was not fixed and therefore not abnormal. In one individual, such a motion could not be recognized and by bending and rotating the head, muscle pains were elicited, suggesting that the asymmetry was abnormal and due to muscle fixation. If active sideways bending of the head shows movement of the atlas and if a demonstrated asymmetric position of the atlas can thus be corrected, then a diagnosis of subluxation cannot be made roentgenologically.—*Samuel Richman, M.D.*

Neck and Chest

Pieri, J., and Casalonga, J. Chondromatose diffuse de la trachée et des bronches. (Diffuse chondromatosis of the trachea and bronchi.) *Presse méd.*, Nov. 27, 1957, *65*, 1933–1935. (From: Chaire de Thérapeutique de la Faculté de Médecine de Marseille, Marseille, France.)

Tracheobronchial chondromatosis presents itself anatomically as an involvement of the trachea and major bronchi by multiple and diffuse cartilaginous tumors which are generally benign. Clinical symptoms, however, may be severe because of the effect on the underlying parenchyma and of obstruction to the discharge of secretions. In addition, there may be complications which are inherent with any tracheobronchial stenosis.

The condition is very rare. The present case is classified as tracheopathia osteochondroplastica of Aschoff-Landsberg. Clinically, the disease is marked by symptoms of gross bronchial irritation, or of stenosis of a large aerial trunk. Most often, the diagnosis is made by bronchoscopy which was also done in the present case because of an episode thought to be due to acute atelectasis. The trachea was involved by a number of buds which on biopsy were found to be cartilaginous islands composed of chondroblasts. Conventional roentgenograms were noncontributory. Laminagrams made in various positions demonstrated a number of very peculiar parietal images with a nodular formation along the length of the trachea. Laminagrams made with a

perpendicular craniocaudal incidence also showed the irregular outline of the trachea. The endobronchial parietal projections were seen best in the transverse axial laminagram. The illustrations are most interesting and should be studied in the original article.—*Marcy L. Sussman, M.D.*

Sprunt, William H., III. The diagnostic accuracy of plain films in bronchiectasis. *South M. J.*, Jan., 1958, *51*, 67–72. (From: The Department of Radiology, North Carolina Memorial Hospital, Chapel Hill, N. C.)

It is the purpose of this paper to emphasize the fact that the diagnosis of bronchiectasis can often be suggested with a high degree of accuracy from abnormalities found in the posteroanterior and lateral roentgenograms of the chest. Confirmation by bronchography is always necessary.

In this study 44 known cases of bronchiectasis were reviewed and five findings were thought to be characteristic of bronchiectasis: (1) Increased pulmonary markings, (2) pleural and diaphragmatic abnormalities, (3) decrease in the volume of the lung, (4) pneumonitis, and (5) ring shadows or "honeycombing."

The increased pulmonary markings are probably due to a peribronchial and perivascular inflammatory process, together with some crowding of the vessels produced by organization and scarring. Eighty per cent of the cases studied revealed increased markings.

Loss of definition of the diaphragm due to pleural thickening or abnormal curvature of the diaphragm was present in 70 per cent of the cases studied. Abnormalities of the diaphragm and increased lung markings were the most common findings in this study, but were also considered the least reliable when found alone.

A decrease in the volume of the lung, varying from a slight but definite crowding of the markings with alteration in position of the fissures to dense triangular opacities with mediastinal shift, was found in 48 per cent of the cases studied.

Some degree of pneumonitis was present in 36 per cent of the cases.

Ring shadows or "honeycombing" vary in appearance from thin-walled cystic areas to whorled poorly defined shadows of irregular thickness of the walls. These were present in 23 per cent of the cases.

It is the author's belief that if one of these findings is present the diagnosis is "possible bronchiectasis." Two of these findings would warrant a diagnosis of "probable bronchiectasis." Three or more of them indicate a "highly probable bronchiectasis." As already stated, bronchographic confirmation is necessary.—*Lysle M. Bach, M.D.*

Anacker, H. Die röntgenologischen Merkmale des Lymphknoteneinbruches in den Bronchus; Zugleich Mitteilung über zwei Fälle einer Bronchusperforation bei Lymphogranulomatose. (The roentgenologic signs of lymph node perforation into a bronchus; simultaneously a report of two cases of bronchus perforation in lymphogranulomatosis.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Nov., 1957, *87*, 588–597. (From: Röntgenabteilung der Chirurg. Univ.-Klinik, Giessen, Germany.)

Knowledge of the syndrome of lymph node perforation into a bronchus is important from a therapeutic standpoint. The correct diagnosis depends on proper roentgen studies with the aid of laminagraphy and bronchography. Bronchoscopy is of value only in the lower parts of the lungs but of no help in the upper lobes.

The following roentgen signs are discussed and illustrated: (1) Stenosis or closure of the bronchus with calcification either distally, laterally or intraluminally; (2) stenosis or closure alone or in combination, but without calcification; (3) closure of bronchus combined with lymph node fistula; and (4) nodular tumor within a bronchus.

Calcification is found most frequently and atelectasis is the leading sign in endobronchial lesions. The latter is absent only when a lymph node perforates into the trachea or a stem bronchus. In these cases, however, the correct diagnosis can be made with the aid of laminagraphy and bronchography. Another significant finding is a hilar lymph node cavity with fistula formation. Localized indentation of a bronchus alone without calcification is inconclusive; but in such instances one has to consider the possibility of tuberculous lymph node perforation, especially when the following characteristic findings are present: (1) History negative for tuberculosis; (2) sudden onset with fever and hemoptysis; (3) typical infiltrate with segmental or lobar atelectasis; and (4) development of a positive sputum.

The material consists of 23 cases with a total of 28 perforations of lymph nodes. Two so-called rare cases with perforation of lymphogranulomatous nodes into a bronchus are also reported. There was bilateral superior mediastinal widening with convexity of the border on one side and concavity on the other side. This latter observation served as a clue for upper lobe atelectasis with underlying encroachment upon the lobar bronchus.—*Ernest Kraft, M.D.*

Siddons, A. H. M. Oil granuloma of the lung; report of three cases. *Brit. M. J.*, Feb. 8, 1958, *1*, 305–307. (From: Surgical Unit, St. George's Hospital, London, England.)

Lipoid granuloma of the lung may be either exogenous (aspiration of mineral, vegetable or animal fats), or endogenous (endogenous fatty substances

occurring in association with bronchial obstruction and generalized disturbance of fat metabolism).

The exogenous type is most common in infants with feeding disturbances, in the elderly with neurologic disorders interfering with the swallowing mechanism, and in patients with chronic esophageal obstruction, such as achalasia of the cardia. Significance of the disease lies in its roentgenologic similarity to carcinoma of the lung. Features which suggest the true nature of the disease are: (1) Minimal, if any, symptoms; (2) location of density in an "aspiration area" of lung; (3) negative bronchoscopic examination; (4) fat droplets in the sputum; (5) etiologic factor (as listed above).

Three cases of exogenous type of oil granuloma are reported. In a seventy-two year old man the habitual use of liquid paraffin as an aperient was the apparent etiologic factor of a right lower lobe granuloma. In a fifty-six year old woman, the history revealed no clue to the cause of a right middle lobe granuloma. A forty-one year old man who had had achalasia treated by myotomy of the cardia had a lobulated granuloma in the right upper and middle lobes. The upper lobe only was removed. In the year following, the granuloma in the right middle lobe increased in size and a new one (presumably) developed in the left upper lobe. This was of interest in view of the previous successful treatment of the achalasia but was probably due to the fact that the esophagus still showed delay in emptying, as demonstrated by a barium meal examination.—*Lois Cowan Collins, M.D.*

MELE, MARIO, and DE MARIA, BENIAMINO. Rilievi pneumoangiografici nella silicosi. (Pneumoangiographic findings in silicosis.) *Ann. radiol. diag.*, 1957, *30*, No. 4, 269–294. (From: Istituto di Semeiotica Medica della Università, Roma, Italy.)

A group of 20 patients incapacitated with silicosis, who had been thoroughly studied with all other available methods, were subjected to pulmonary angiography.

The principal vascular changes noted were: (1) Changes in form, caliber and distribution of the large arterial and venous vessels; (2) nonvisualization of arterio-capillary vessels in certain areas of the lung parenchyma; (3) shortening in time of the pulmonary circulation; and (4) prolongation in time of the pulmonary circulation.

In those patients in whom the pulmonary circulation time was shortened and who had clinical evidence of cyanosis, oxygen administration did not prove beneficial. It was presumed in these cases that a vascular shunt developed which did not permit proper capillary filling or function, resulting in pulmonary hypertension.

The authors believe that this method may be used as an additional study to properly evaluate the incapacity of these patients and the grade of severity of their disease.

The 20 cases studied are reported in detail. Several illustrations are included in this article which are convincing in showing the changes of the vascular pulmonary circulation as described by the authors. —*Peter E. Russo, M.D.*

VAN DE VELDE, E., VAN DER STRAETEN, M., and VERSTRAETEN, J.-M. La séquestration pulmonaire. (Pulmonary sequestration.) *J. belge de radiol*, 1957, *40*, No. 5, 593–612. (From: Service de Radiodiagnostic and Service de Médecine Interne, Université de Gand, Belgium.)

A review of the medical literature on pulmonary sequestration is given. The condition is a double anomaly in that a bronchial branch is developed separate from the normal tracheobronchial tree, and the separated segment of lung is supplied by an anomalous artery from the aorta. The mass of bronchopulmonary tissue is thus nonfunctioning and develops one or more cysts, which tend to become infected. The sequestrated segment may be "intralobar," that is, it is contained between the normal lung and the pleura of the affected lobe, or it may be "extralobar" and be contained in its own pleural covering between the diaphragm and the inferior lobe or even under the diaphragm.

The venous return is toward the pulmonary veins in intralobar sequestration and toward the azygos system in extralobar sequestration. Associated congenital anomalies are more frequent in the latter. Roentgenologically, one sees a consolidated segment with one or more cystic areas frequently associated with a lower lobe. Laminagrams may show the aberrant artery. Bronchography usually reveals the lack of communication with the bronchial tree.

Two cases are presented with roentgenologic features discussed.—*Charles M. Nice, Jr., M.D., Ph.D.*

LUPU, N. GH., and VELICAN, C. La sclérose pulmonaire tabaque. (Pulmonary sclerosis due to use of tobacco.) *Presse méd.*, Dec. 25, 1957, *65*, 2184–2187. (Address: N. Gh. Lupu, Therapeutics Institute of the R.P.R. Academy, Bucharest, Romania.)

Experimental and clinical investigations were carried out with a view to demonstrating the existence of pulmonary sclerosis originating from tobacco smoke.

The *etiologic investigations* showed that the prolonged inhalation of tobacco smoke by laboratory animals regularly induced a diffuse fibrosis of the respiratory parenchyma and pleura which was most developed in the alveolar walls.

The *pathogenic investigations* disclosed that the

increase in the pulmonary histamine level due to smoke inhalation seems to be the most significant sclerogenous mechanism. An injection of antihistaminic substances prior to every inhalation prevented or notably delayed development of the sclerosis.

The *clinical investigations* revealed that a notable proportion of inveterate tobacco consumers (57 per cent) reached the stage of pulmonary sclerosis. By roentgenologic, spirometric, hematologic, and biochemic examinations it was possible to discern the evolutive characteristics of the disease, which is usually classified as physiologic sclerosing emphysema of old age.—*Frank A. Riebel, M.D.*

Winter, Benjamin. (Los Angeles, Calif.) Pulmonic stenosis produced by compression of heart by anterior mediastinal tumor. *Am. Heart J.*, Jan., 1958, *55*, 18–26.

Anterior mediastinal tumors are not unusual in the field of thoracic surgery. It is, however, unusual for such a tumor to cause compression of the heart. Localized compression of the pulmonary artery simulating pulmonic stenosis is particularly uncommon and few cases have been reported. The author reports such a case. A male, aged twenty-one, was admitted with a week's history of "a terrible pain" beneath the upper sternum and associated dyspnea. The significant findings in the patient's past history were shortness of breath and "asthmatic attacks" since birth. Tolerance to exercise had always been limited by shortness of breath. School and insurance examinations revealed no previous evidence of a cardiac murmur. There was no history of cyanosis. Immediate digitalization with oxygen administration was effective in controlling this episode.

The significant physical findings were limited to the heart. In the second and third intercostal spaces to the left of the sternum there was a Grade II harsh systolic murmur. The murmur was transmitted into the neck and heard in both the right and left interscapular areas.

Roentgenographic examination revealed normal peripheral lung markings, borderline enlargement of the heart, and what was considered to be marked dilatation of the main pulmonary artery and its branches. There was, however, a somewhat puzzling, vague, double contour shadow in the area of the pulmonary conus.

Cardiac catheterization indicated changes in pressures across the pulmonary valve consistent with the clinical diagnosis of pulmonary stenosis.

In spite of the apparently conclusive results of the cardiac catheterization, there was still doubt as to the diagnosis. The possibility was raised of an aneurysm of the sinus of Valsalva with bulging into the pulmonic orifice or actual compression and distortion of the pulmonic valve, simulating pulmonic stenosis with a low-pressure differential across the valve.

Angiocardiography was recommended. This procedure demonstrated that the pulmonary artery and its main branches were normal. The superior mediastinal shadow was superimposed over the great blood vessels but never opacified, indicating that this shadow was not of vascular origin but represented an anterior mediastinal mass.

The patient was explored and a large lobulated thymic tumor weighing 1,089 gm. was removed. Microscopically, the tumor showed the typical pleomorphic pattern of Hodgkin's disease. Following a course of radiation therapy, the patient was discharged and has remained well since.

Review of the literature discloses only one case, in which a similar murmur was produced by pressure on the pulmonary artery by a mediastinal malignant teratoma and in which surgical removal of the tumor caused disappearance of the murmur.—*William C. MacCarty, Jr., M.D.*

Eich, Robert H., Citrin, Yale, Schreier, Arthur, and Lyons, Richard H. Use of a quantitative electrokymograph in evaluation of myocardial contractility. *Am. J. M. Sc.*, Dec., 1957, *234*, 631–639.

In this country the electrokymograph has found very limited use, mostly for timing cardiac events, and for depicting left atrial changes. The present contribution represents a further refinement in calibration of the apparatus and its application to the study of myocardial contractility.

The height of the electrokymogram from its peak to its nadir is called the recorded border motion. The known calibration motion is the distance that the entire electrokymographic unit is moved during calibration, and corresponds to the number of the calibration stop previously set. Two millimeters was usually used. The recorded calibration motion is the distance of upward displacement of the baseline of the electrokymogram during the calibration maneuver. The calibration factor is obtained by dividing the recorded calibration motion by the known calibration motion. The absolute motion of the left ventricle is the recorded border motion divided by the calibration factor.

To obtain velocity, the slope of the mid-point of the ejection phase of the electrokymogram was extended for 1 sec. and expressed in millimeters per second. This slope divided by the calibration factor yields the velocity index of systole which is felt to be a representation of the true maximum velocity of contraction.

The results of exercise on the various cardiac measurements in 6 normal subjects are recorded. All subjects showed a 2 to 3-fold increase in the velocity index, and a 1½ to 2½-fold increase in the amplitude of border motion. While these two functions increased during exercise in a parallel fashion, systolic duration changed minimally, if at all.

Further data illustrate the results of exercise on the cardiac measurements in 10 subjects with arteriosclerotic or hypertensive heart disease. Since most of these patients were in atrial fibrillation with extremely variable ventricular rates and rhythm, the ventricular rate and systolic duration were not felt to be amenable to ready analysis. There was a varying response to exercise in the patients with heart disease. In some, the normal expected increase in velocity index did not occur.

Although the noncalibrated electrokymograph has not proved of great value in the assessment of the physiologic state of the myocardium, it was hoped that a calibrated machine would extend its range of usefulness. With a calibrated machine, correction can be made for changes in amplitude due to variations in roentgen ray output and gain from person to person. The authors' modification of the basic apparatus of Morgan and Sturm when checked by an artificial border appeared to be calibrated. Its usefulness on a clinical level was then evaluated. It soon became apparent that many of the limitations of the noncalibrated electrokymograph were still present. Only the ejection phase of systole with its well established time limits could be subjected to quantitative analysis. Variations in the functional state of the myocardium should be measurable in terms of changes in myocardial "contractility." The term "contractility" includes both the extent and the rate of myocardial shortening. The slope of the midportion of ejection is used as an index of velocity of contraction, and thus presumably of myocardial contractility.

The same limitations, due to heart size, shape, and muscle arrangement, would still hold for the resting velocity. Therefore, it is not unexpected that the resting velocity of the abnormals falls into the wide range of resting normal values.

It is suggested that the study of the velocity of contraction may prove a useful measure of not only the degree of compensation of the failing heart, but also of the effect of various drugs and exercise on one aspect of myocardial function.—*Stephen N. Tager, M.D.*

Mayer, Florence E., Nadas, Alexander S., and Ongley, Patrick A. Ebstein's anomaly; presentation of ten cases. *Circulation*, Dec., 1957, *16*, 1057–1069. (From: The Sharon Cardiovascular Unit of the Children's Medical Center and the Department of Pediatrics, Harvard Medical School, Boston, Mass.)

The authors present selected findings from the histories, physical examinations and laboratory studies of 10 patients of their own with the above affliction, then comment upon these aspects of the cases found in the literature. They emphasize the importance of clinically differentiating this condition from those amenable to surgery, as cardiac catheterization and exploratory surgery carry a very definite hazard here.

In 9 of the cases, increased fatigability and mild dyspnea were nearly constant findings after the age of one year, and cyanosis had been present in all but one, although age of onset varied. The most consistent findings on physical examination were a systolic thrill, triple or quadruple rhythm, diminished pulmonary second sound and systolic and diastolic murmurs parasternally on the left and at the apex.

Phonocardiographic findings were quite similar in each case. Electrocardiograms showed tall, peaked or broad P waves in leads II, V_1 and V_2 and right bundle branch block as nearly constant features.

Roentgenographically, right sided cardiomegaly was present in all, with typically a narrow base and small aorta, poorly visualized pulmonary artery and decreased pulmonary vascular markings. Two patients studied by angiocardiography had huge, slowly emptying atrial chambers, suggested right to left shunts and in one a poorly filling pulmonary artery.

Additional information was contributed by cardiac catheterization in 4 cases, although one death occurred during this procedure and one during angiocardiography.

Clinically, 6 patients are living with minimal symptoms; 4 have died. In each of the latter, autopsies revealed hearts 2 to 3 times normal size with markedly dilated right atria, patent foramen ovale, and misplaced tricuspid valve leaflets varying in size and location within the dilated atrium.

In reviewing the literature and correlating this with their own cases, the authors emphasize the following clinical points which are of diagnostic value: (1) *History:* Usually mild symptoms with cyanosis, dyspnea, fatigability and bouts of palpitation being common. (2) *Physical examination:* Normal physical growth, frequently cyanosis, quiet cardiac impulse with systolic thrill, triple or quadruple rhythm, diminished P_2, and combined systolic and diastolic murmurs at the left sternal border or apex. (3) *Phonocardiography:* Delayed, normally intense first sound, systolic murmur of moderate intensity and medium frequency, a presystolic murmur at the left border of the sternum and apex. (4) *Electrocardiography:* Tall P waves, prolonged A-V conduction, right bundle branch block and low amplitude right ventricular potentials. (5) *Roentgenography:* Cardiomegaly on the right, narrow base, diminished pulmonary vascular markings and poorly delineated pulmonary artery. (6) *Angiocardiography:* Huge right atrium with delayed emptying, poorly opacified pulmonary radicles and frequent evidence of right-to-left shunts. (7) *Cardiac catheterization:* Large atrium, displacement of the tricuspid valve to the left, moderately elevated right atrial pressure, normal right ventricular systolic pressure and absence of a significant gradient across the pulmonary valve.—*William C. MacCarty, Jr., M.D.*

Prioton, J.-B., Thévenet, A., Pelissier, M., Puech, P., Latour, H., and Pourquier, J. Cardiographie ventriculaire gauche par cathétérisme retrograde percutane fémoral; technique et premiers résultats. (Left ventricular cardiography by percutaneous retrograde femoral catheterization; technique and first results.) *Presse méd.*, Nov. 27, *65*, 1948–1951. (From: Service de Radiologie du Centre hospitalier régional de Montpellier, Montpellier, France.)

The first systematic study of left ventricular injection in man was made in 1951 by Ponsdomenech and Nuñez, who used a retroxiphoid puncture. They found the procedure useful in the diagnosis of mitral insufficiency. The work was confirmed by Smith *et al.* in 1954. Subsequent workers introduced the opaque material through the left atrium.

The practice of thoracic aortography by retrograde catheterization demonstrated to the present authors, as to others, that it was possible to pass the aortic valve with impunity. The present work on left ventricular cardiography is based on injection through this catheter.

A polyethylene catheter with a flexible metal conductor is passed through the femoral artery up to the region of the aortic valve. Sometimes it passes immediately into the left ventricle, but more often a few forward thrusts and retreats are necessary. Pressure to force the catheter through is useless and dangerous. Experience has shown the authors that a slight contact with the valve is all that is necessary since cardiac contractions and aortic flux carry it through.

The authors use an apparatus permitting three exposures per second. A collimating cone and fine grid are valuable. The patient is placed in the right anterior oblique position with the tube tilted 20° toward the head. The opaque substance injected is vasurix 25 or 38. Twenty cc. are injected under about 4 kg. pressure. Immediately after each seriography, 5 to 10 cc. of 1 per cent novocain is injected through the catheter which is also obturated to avoid clotting.

This method permits the study of the morphology and movement of the left ventricle and its structures. The ventricular and atrial chambers, the mitral apparatus and its pillars, the aortic orifice and the sigmoid sinuses are visualized. The procedure is well tolerated even in patients in poor condition or advanced age. There are no clinical manifestations when the catheter is advanced. About ten seconds after the end of the injection, there may be a transient bradycardia disappearing in about one minute. The procedure is ordinarily not feasible in children under the age of six years. It would not be successful if there is an aortic obstruction such as atheroma at the bifurcation. In 2 cases, the aortic valve could not be passed.

In the congenital group, interventricular communications are well studied by this method. It is useful also in the study of persistent common atrioventricular canal with its septal defect and congenital mitral insufficiency. In the acquired cardiac group, mitral insufficiency is particularly worthy of notice. Lesions of the aortic valve also may be studied.—*Marcy L. Sussman, M.D.*

Cruickshank, D. Barron. Primary intrathoracic neurogenic tumours. *J. Fac. Radiologists*, Oct., 1957, *8*, 369–380. (From: Papworth Hospital, Cambridge, England.)

Neurogenic tumors, defined as those arising from nerves, and those arising from potential nerve tissues, include benign and malignant lesions. In the benign group one finds the solitary and the multiple (von Recklinghausen's disease) neurofibromata arising from the nonspecific nerve sheath, neurilemmomata, arising from the lemmocytes of the specific nerve sheath, and the ganglioneuromata, arising from the ganglia of the sympathetic chains and of the posterior spinal roots. The malignant tumors consist of the neurogenic sarcomata (arising from the neurofibromata), the malignant variant of the neurilemmomata (rare and difficult to differentiate from neurogenic sarcoma) and the neuroblastoma (arising from the ganglioneuroma). In addition, in the development of the nerve tissues from the parent ectodermal-neural crest cells there is an intermediate stem cell (sympathogonia) which differentiates into (1) the neuroblast ganglion cell forming the ganglioneuroma, and (2) chromaffin cells. These latter may give rise to a rare benign tumor, the pheochromocytoma, and to a malignant tumor, the pheochromoblastoma. Chromaffin tissue is concentrated in certain para-aortic structures,—the organs of Zuckerkandl, the carotid body and the ductus arteriosus body as well as in the adrenals. Mediastinal pheochromocytomas may arise from chromaffin tissue in the ductus arteriosus body, and closely resemble bronchial adenomata.

Benign neurogenic tumors constitute the commonest mediastinal abnormality. They occur most frequently (72 to 92 per cent in various reported series) in the posterior mediastinum, probably because the bulk of thoracic neural tissue lies in the posterior mediastinum or paravertebral gutter. The commonest type of benign neurogenic tumor is the neurofibroma, followed by the ganglioneuroma, and the neurilemmoma.

Most of the primary malignant neurogenic tumors occur in early childhood, and sarcomatous degeneration of apparently originally benign forms manifests itself at an earlier age than do most of the benign neurogenic tumors. Malignancy is found in an average of 11.6 per cent of primary intrathoracic neurogenic tumors, according to various authors.

A small but definite proportion of intrathoracic

neurogenic tumors occurs in the anterior mediastinum, in fissures and bronchi of lungs, in the diaphragm, in the anterior chest wall, in the neck (vagal sheath) and in the brachial plexus (Pancoast syndrome).

Statistically it is highly probable that a posterior mediastinal shadow will represent a neurogenic tumor and that a non-posterior mediastinal shadow will not derive from a neurogenic tumor. Signs and symptoms of irregular adrenalin secretion would favor a pheochromocytoma; neurofibromatosis (von Recklinghausen's disease) would strongly suggest a neurogenic tumor; metastasis from a mediastinal tumor (if available for biposy) will probably clinch the diagnosis; and in a non-posterior mediastinal lesion in a female patient the statistical probabilities would be more in favor of a neurogenic tumor, being twice as frequent in women as in men.—*Samuel G. Henderson, M.D.*

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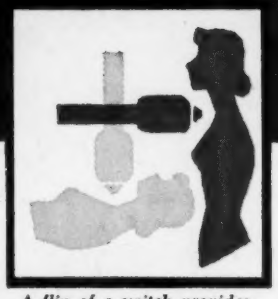

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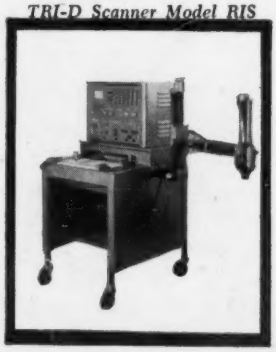

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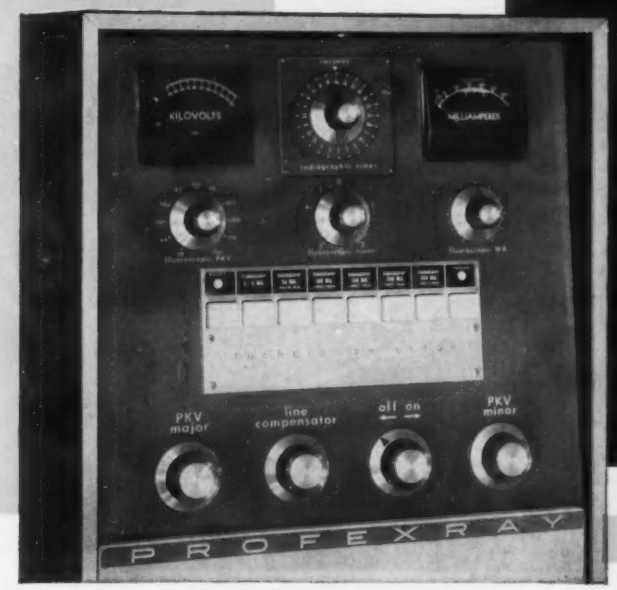

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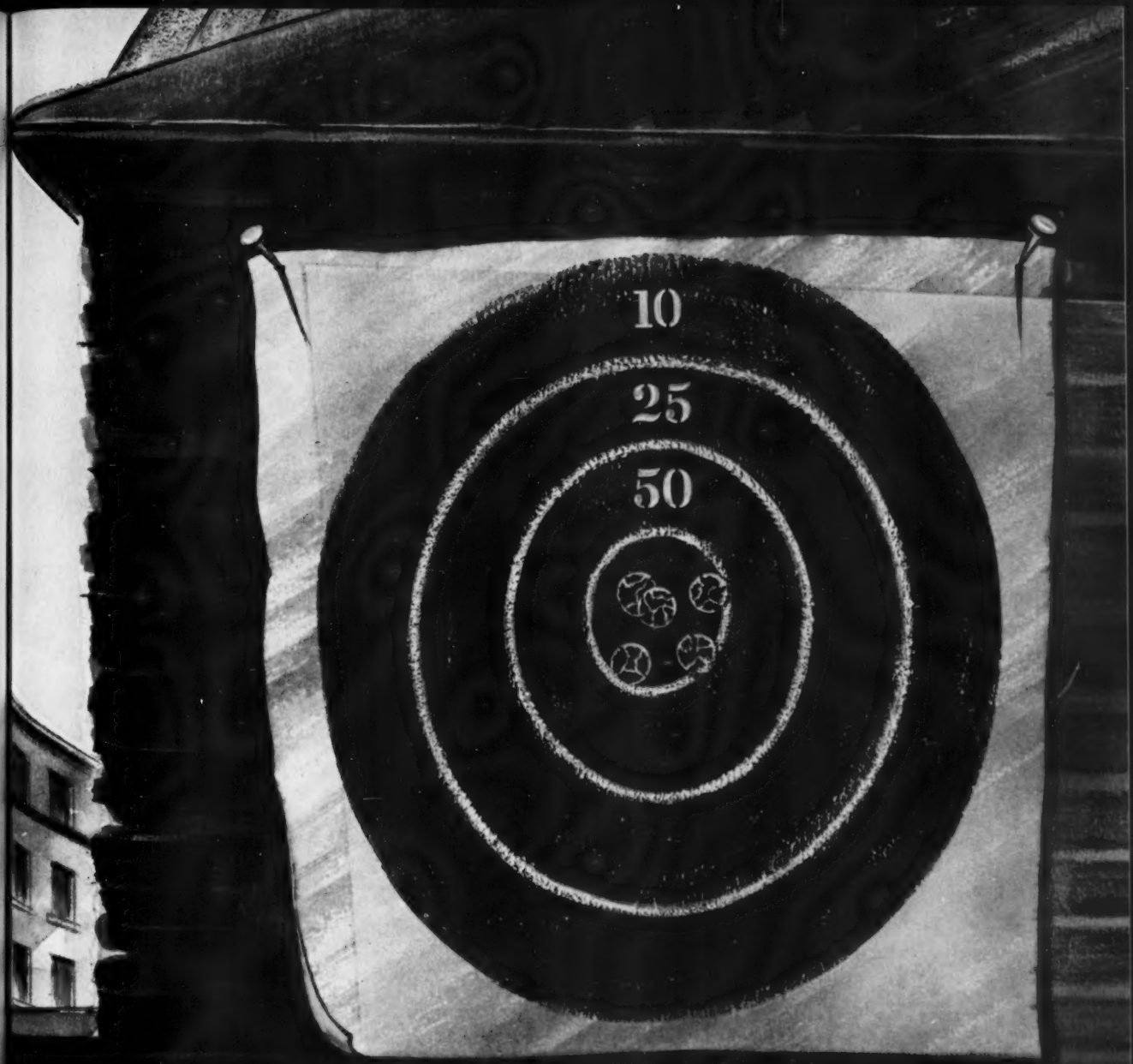

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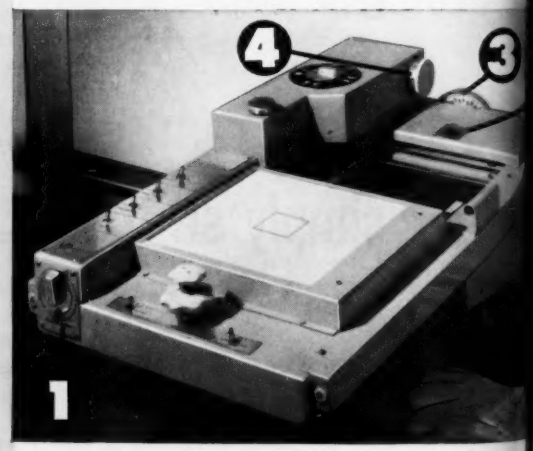

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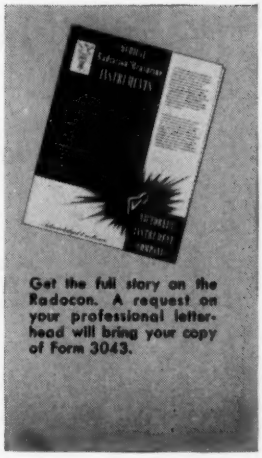

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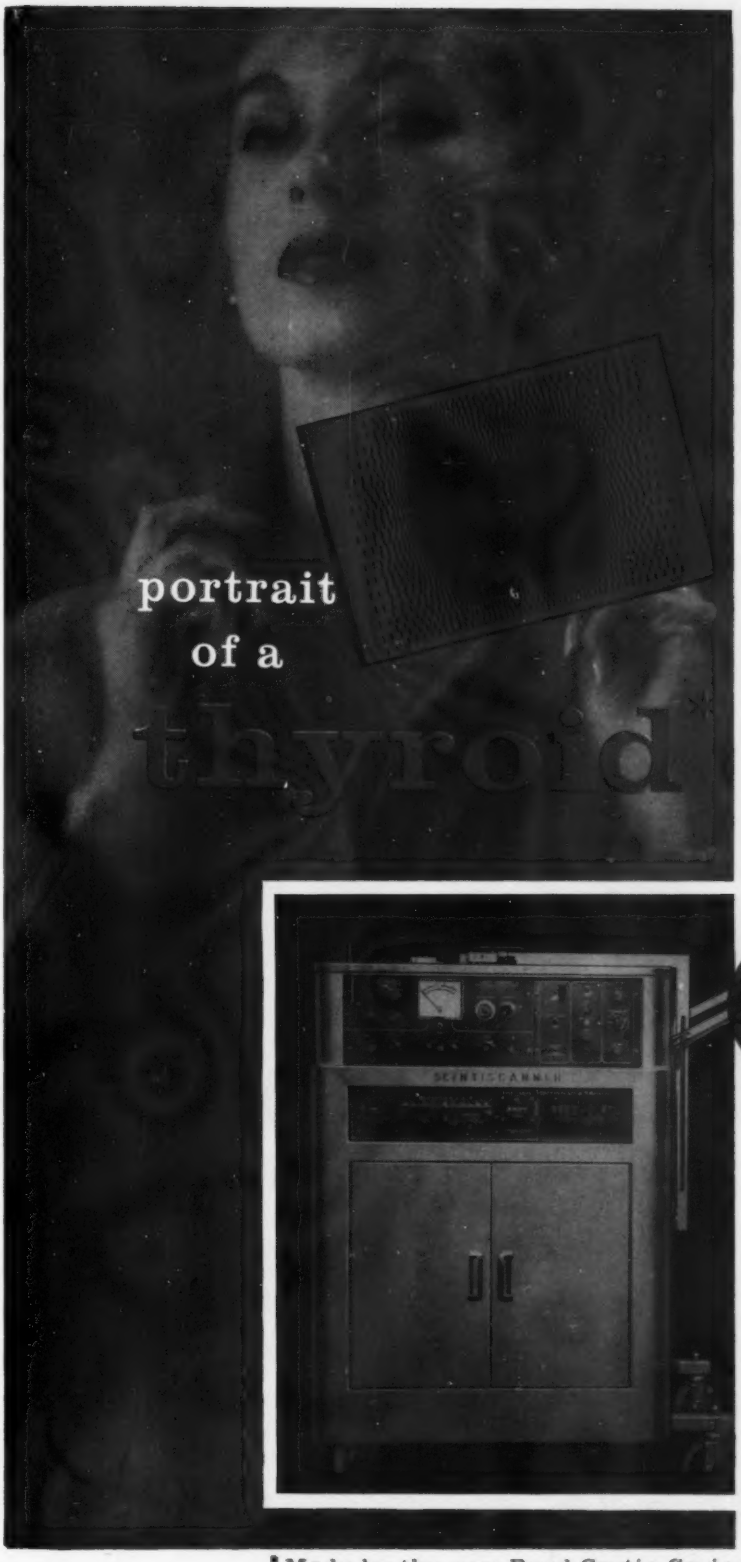

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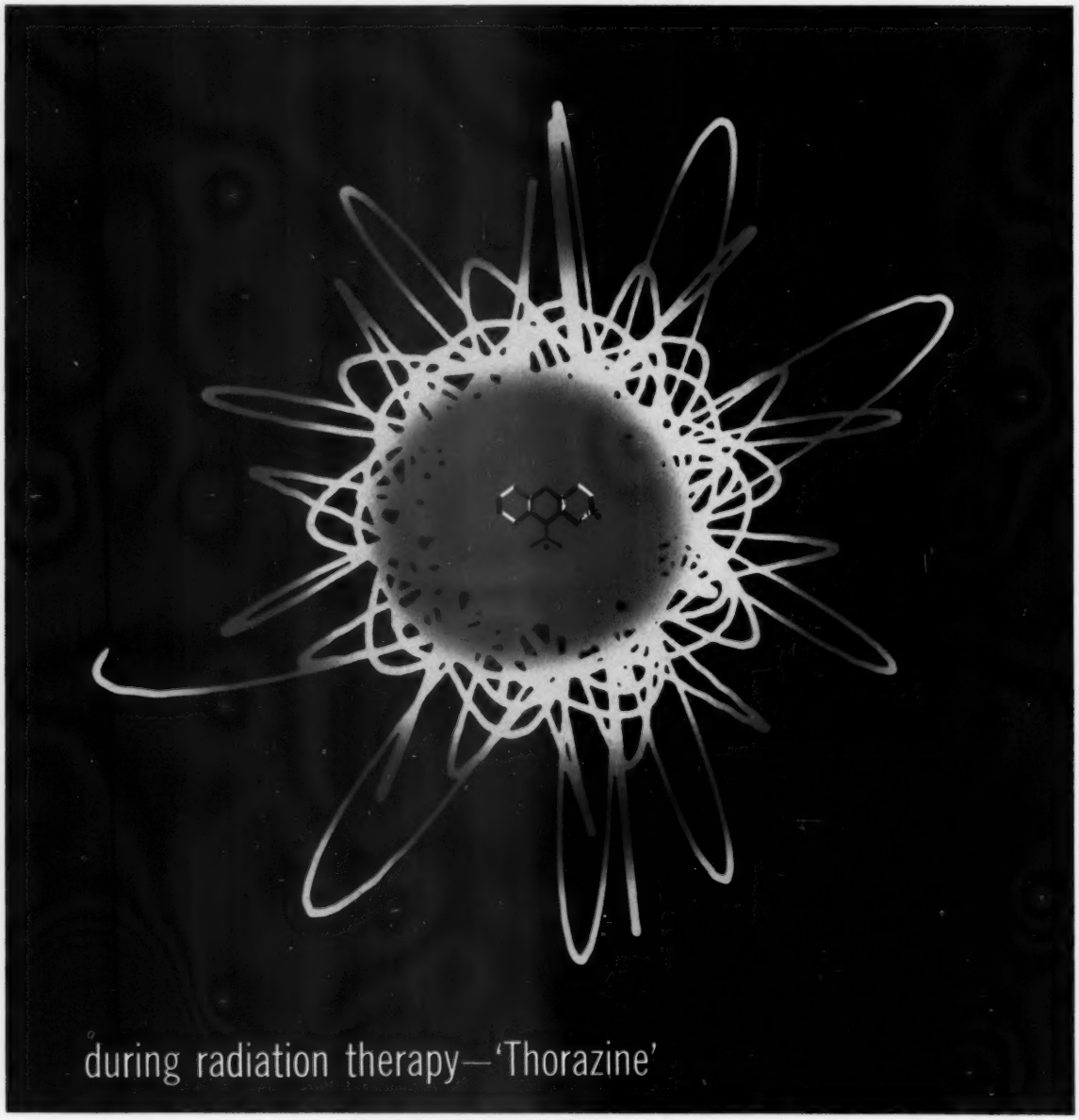

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1. Nesbit, Reed: Editorial, Radiology and Its Contribution to Urology, The American Journal of Roentgenology, 75:995 (May, 1956).

*Dr. V. H. Wallingford of Mallinckrodt Chemical Works synthesized this compound known as Urokon Sodium Brand of Sodium Acetrizoate in 1945.

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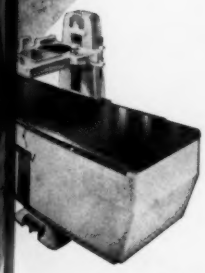

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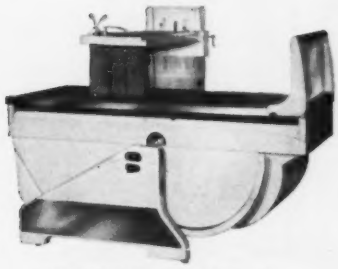

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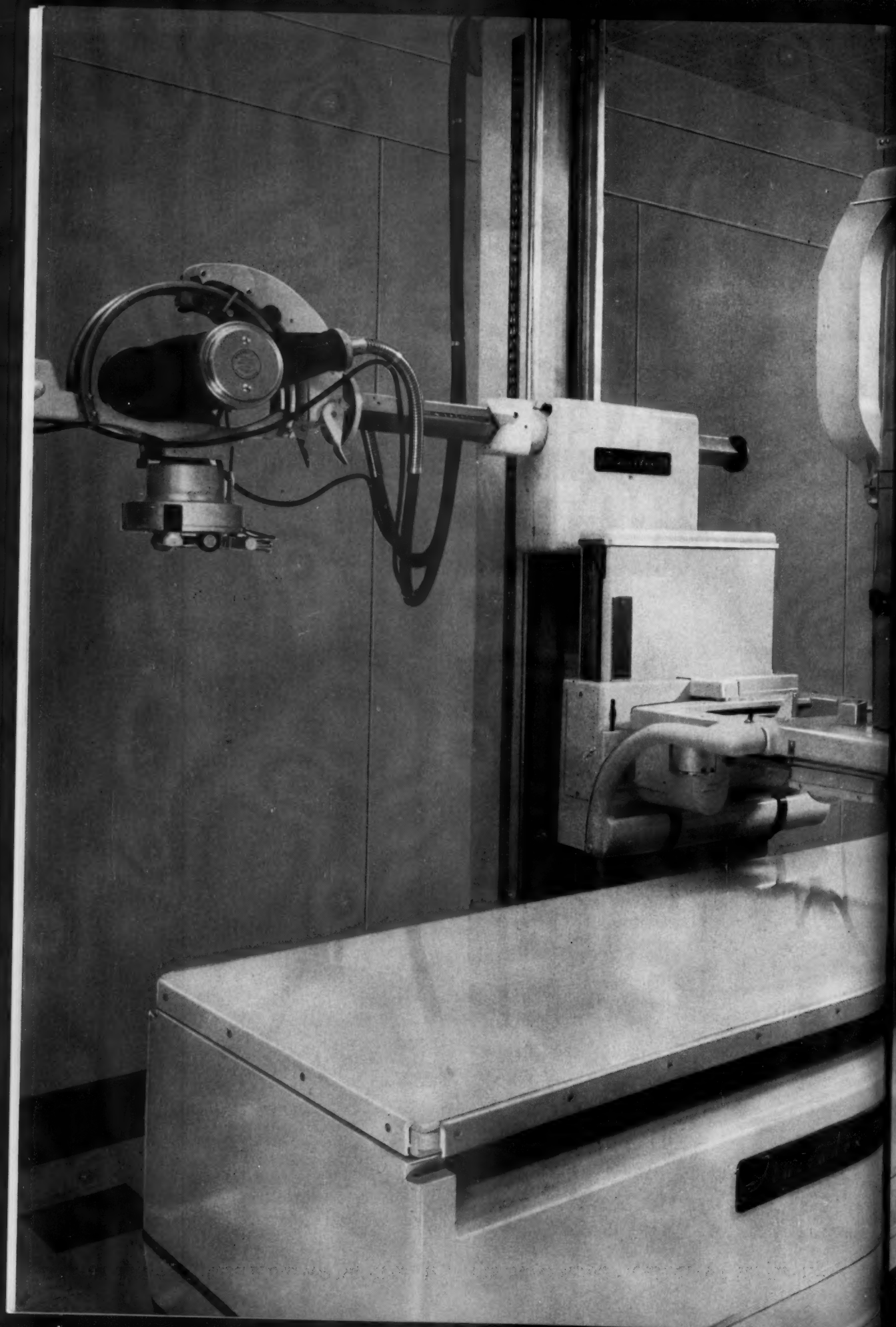

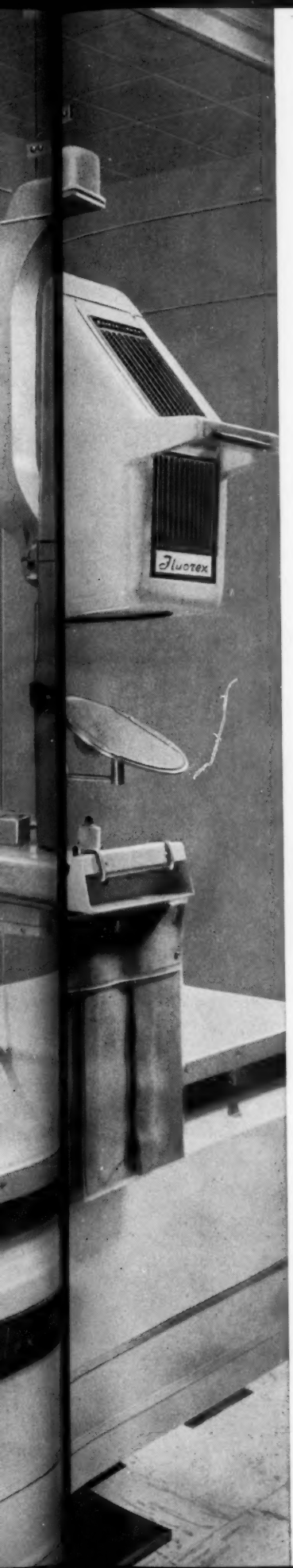

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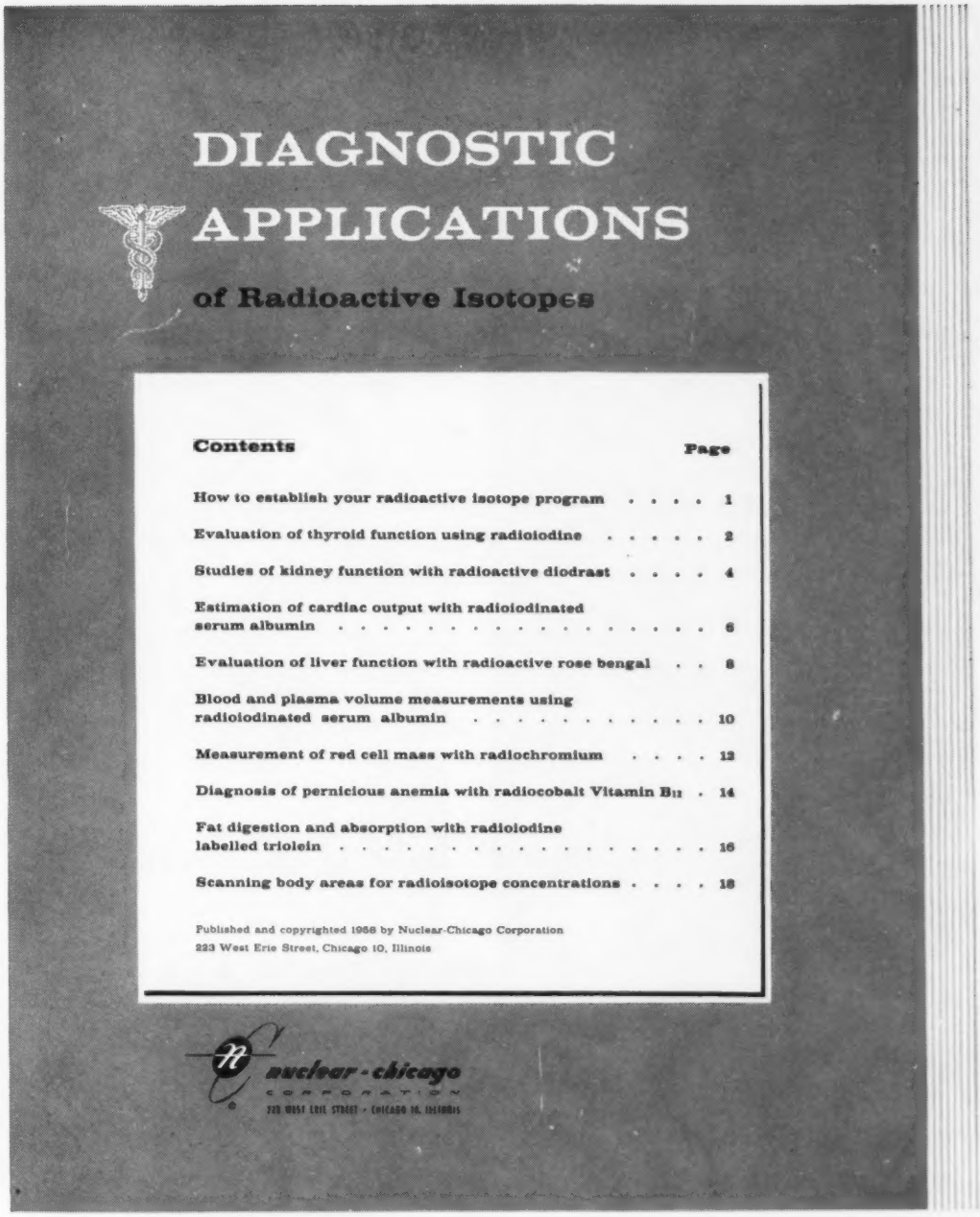
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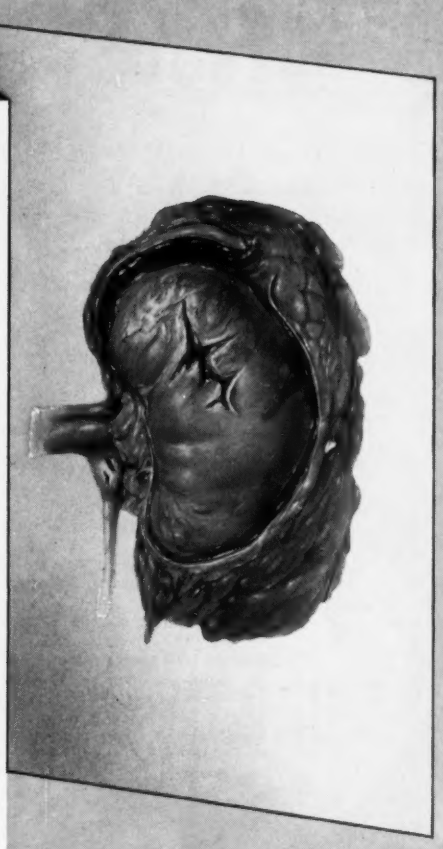

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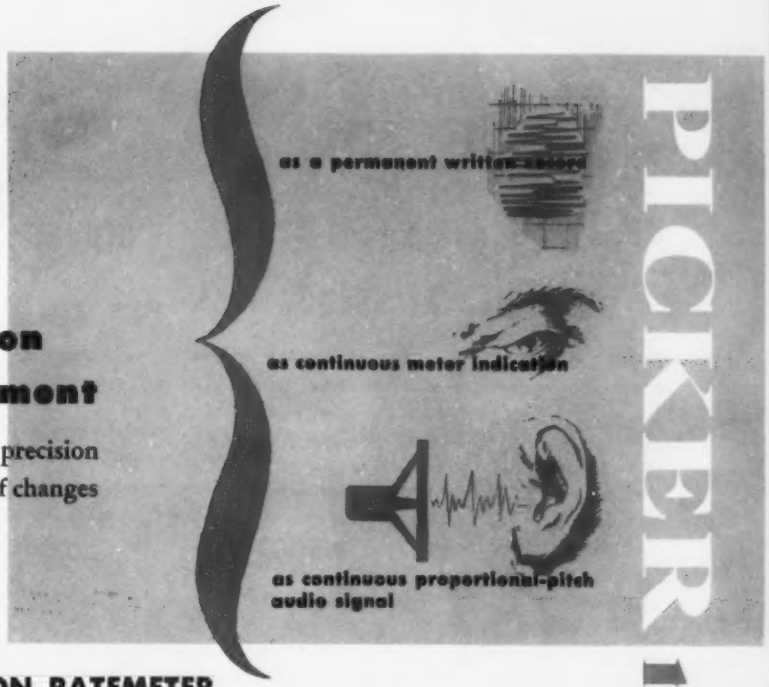

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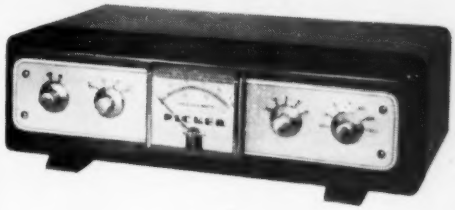

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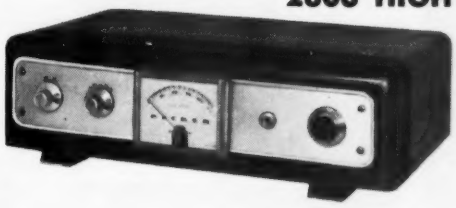

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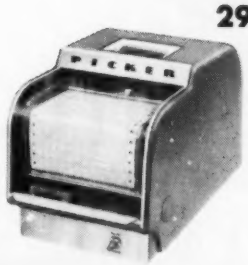

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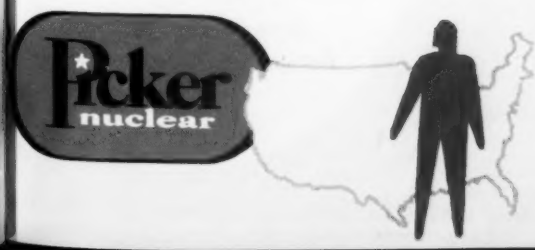

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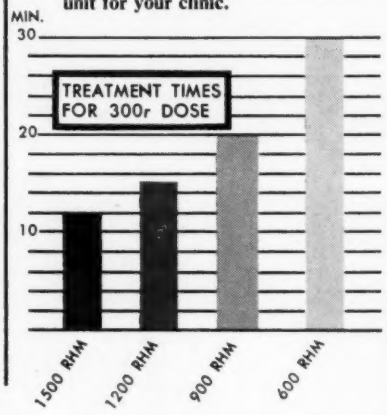

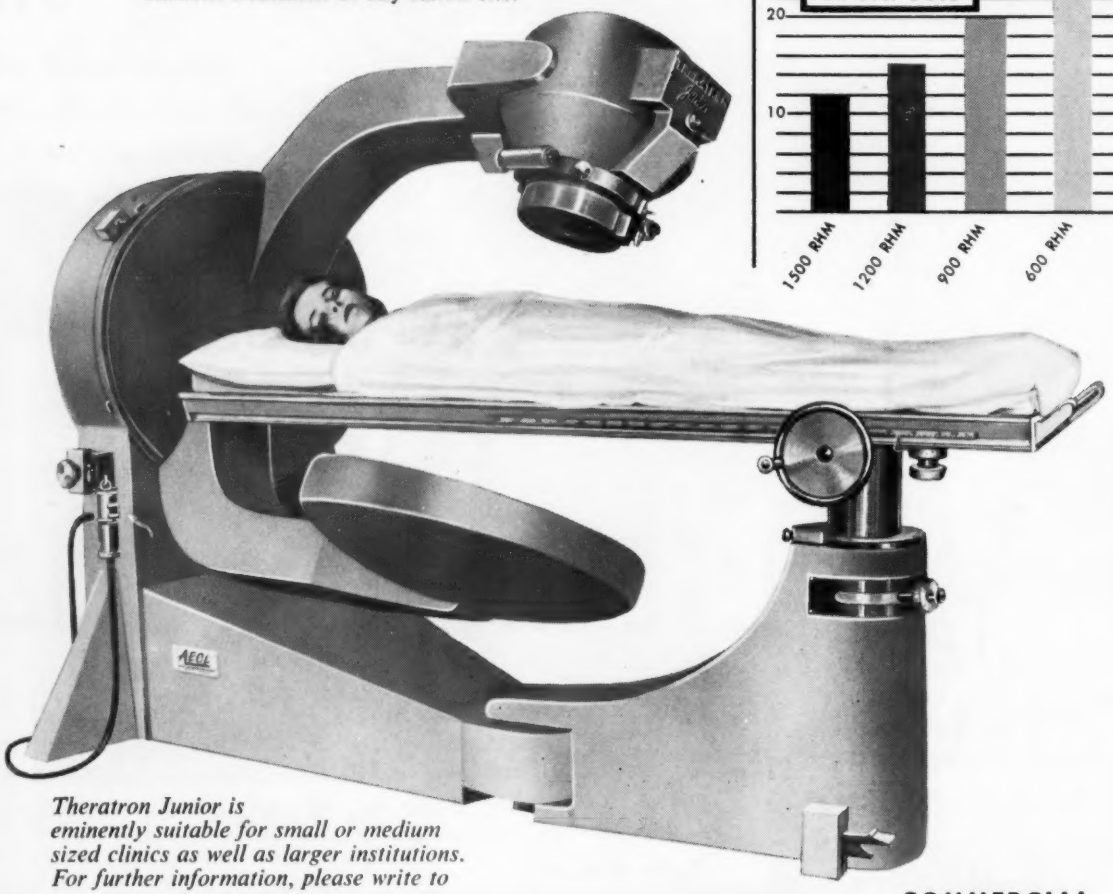

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1. Reeves, R. J.: Southern M. J. 50:1377 (Nov.) 1957.
2. Shehadi, W. H.: Am. J. Gastroenterol. 28:236 (Sept.) 1957.
3. Sachs, M. D.: J. Internat. Col. Surgeons 27:681 (June) 1957.

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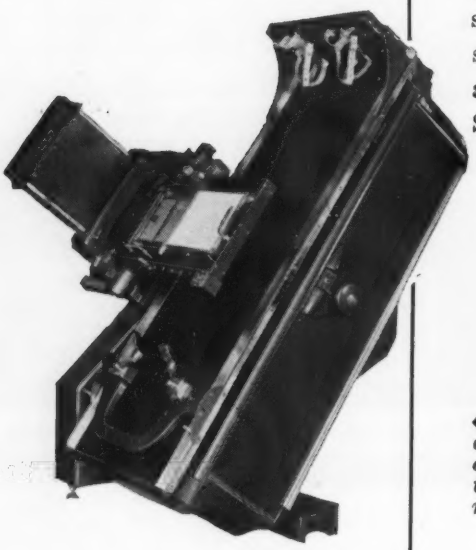

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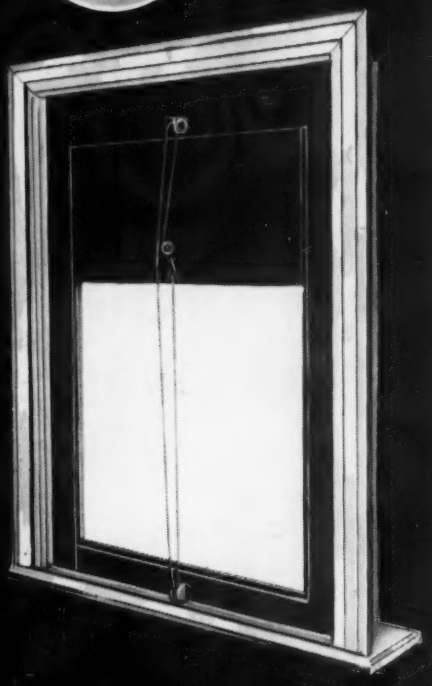

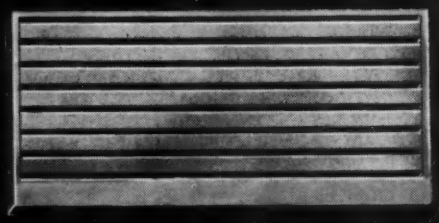

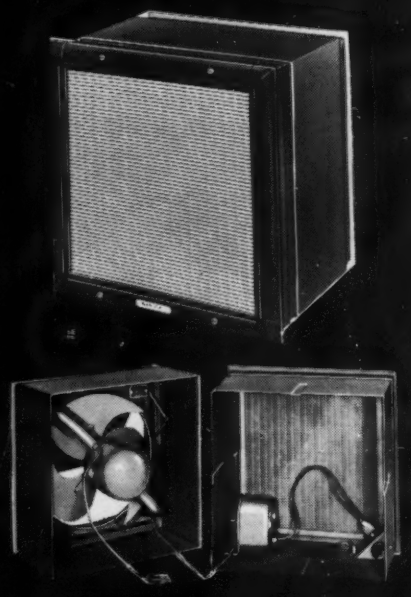

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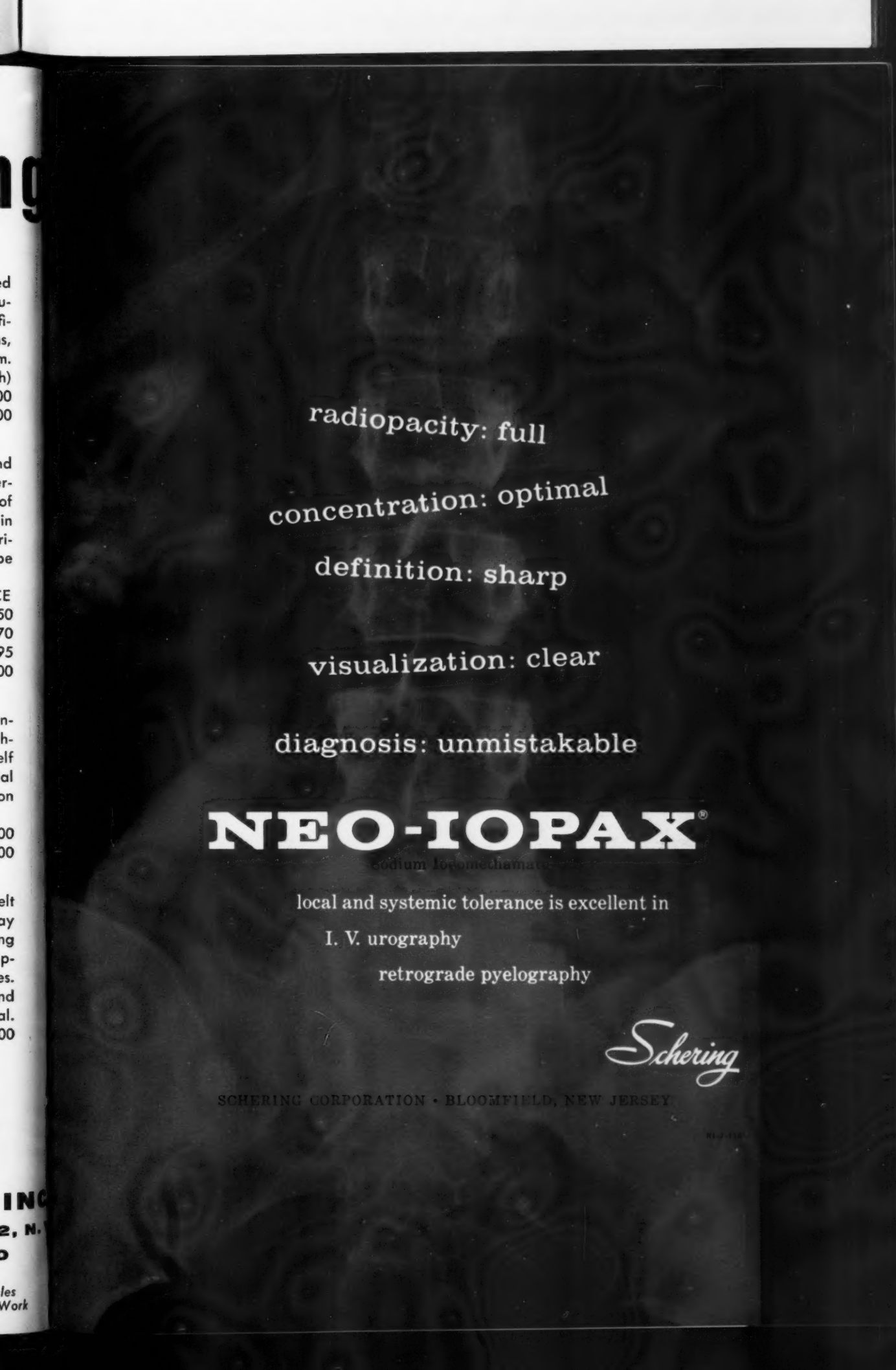
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PIGMENTED VILLONODULAR SYNOVITIS
. . . 3 aspects

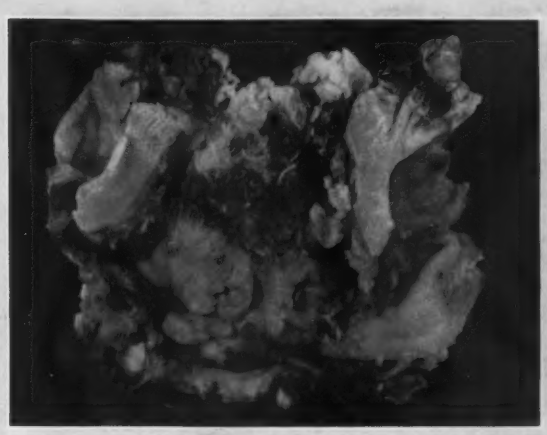

Figure 2 *(above)*—Photograph of a portion of the resected synovium with attached menisci from the case shown in Figure 1. Note the deep brownish color of parts of the villously hypertrophied synovium.

Figure 1 *(above)*—Lateral radiograph of knee area in a case of pigmented villonodular synovitis in a man of 53 years. Note the lobulated soft-tissue masses posteriorly and the effects of invasion of the patella and the femoral condyles by lesional tissue.

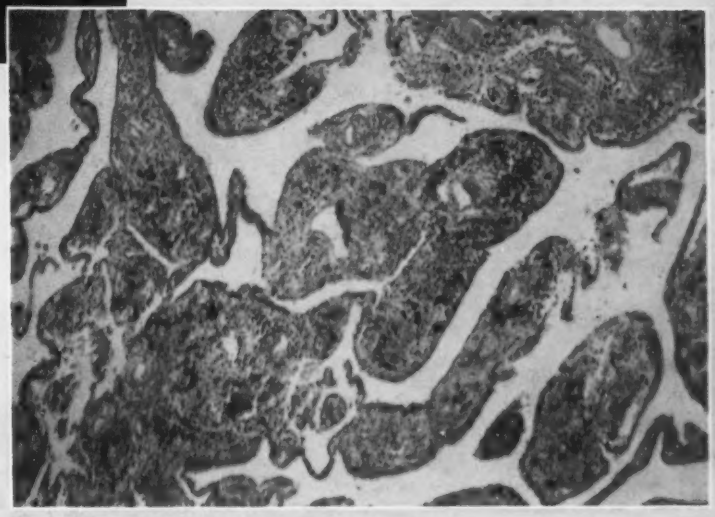

Figure 3 *(right)*—Photomicrograph (x 25) showing a tissue area in a villonodular synovitis in which the proliferated villi are matted together. The brownish discoloration of the tissue is due to hemosiderin pigment.

Turn page for data on Synovial Osteochondromatosis . . . 3 aspects

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SYNOVIAL OSTEOCHONDROMATOSIS . . .
3 aspects

Figure 1 *(above)*—A lateral radiograph from a case of synovial osteochondromatosis of the knee. Note the faint opacities in the suprapatellar pouch area and in the posterior compartment.

Figure 2 *(above)*—Photograph showing the synovial surface of the suprapatellar pouch. Note the cartilaginous excrescences, many of which are protruding from the surface.

Figure 3 *(right)*—Photomicrograph (x 3) of representative section prepared from lesional tissue shown in Figure 2. Note the numerous islands of cartilage within the synovial membrane. Some are agglomerated and are protruding into the pouch.

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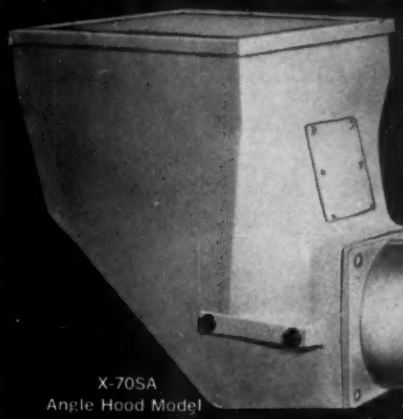

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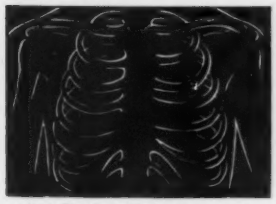

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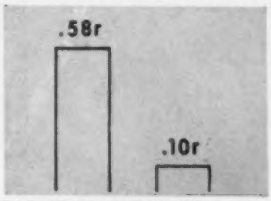

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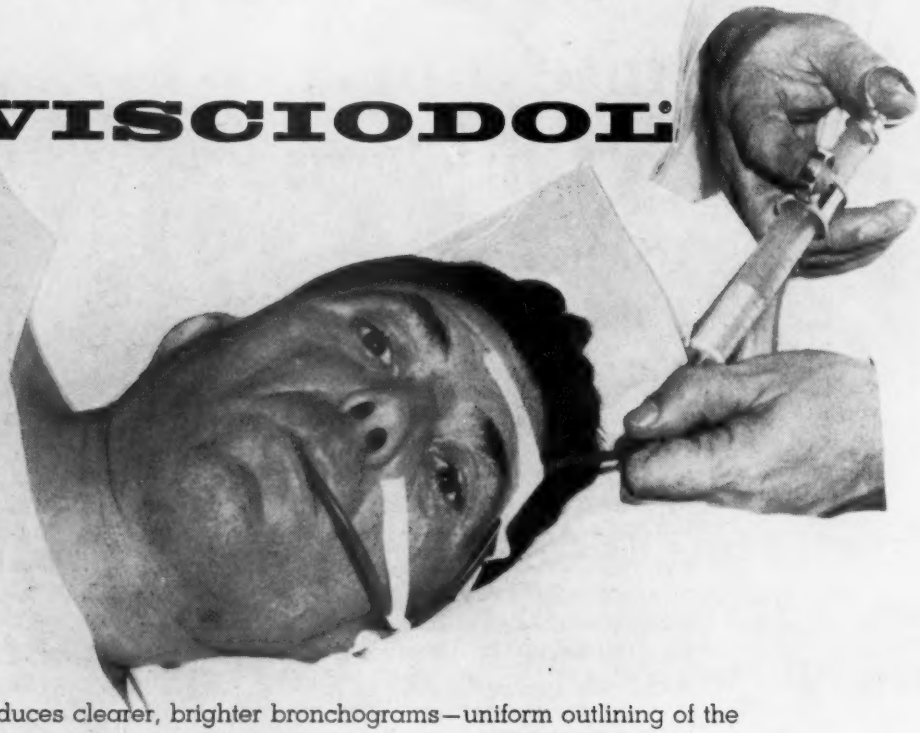

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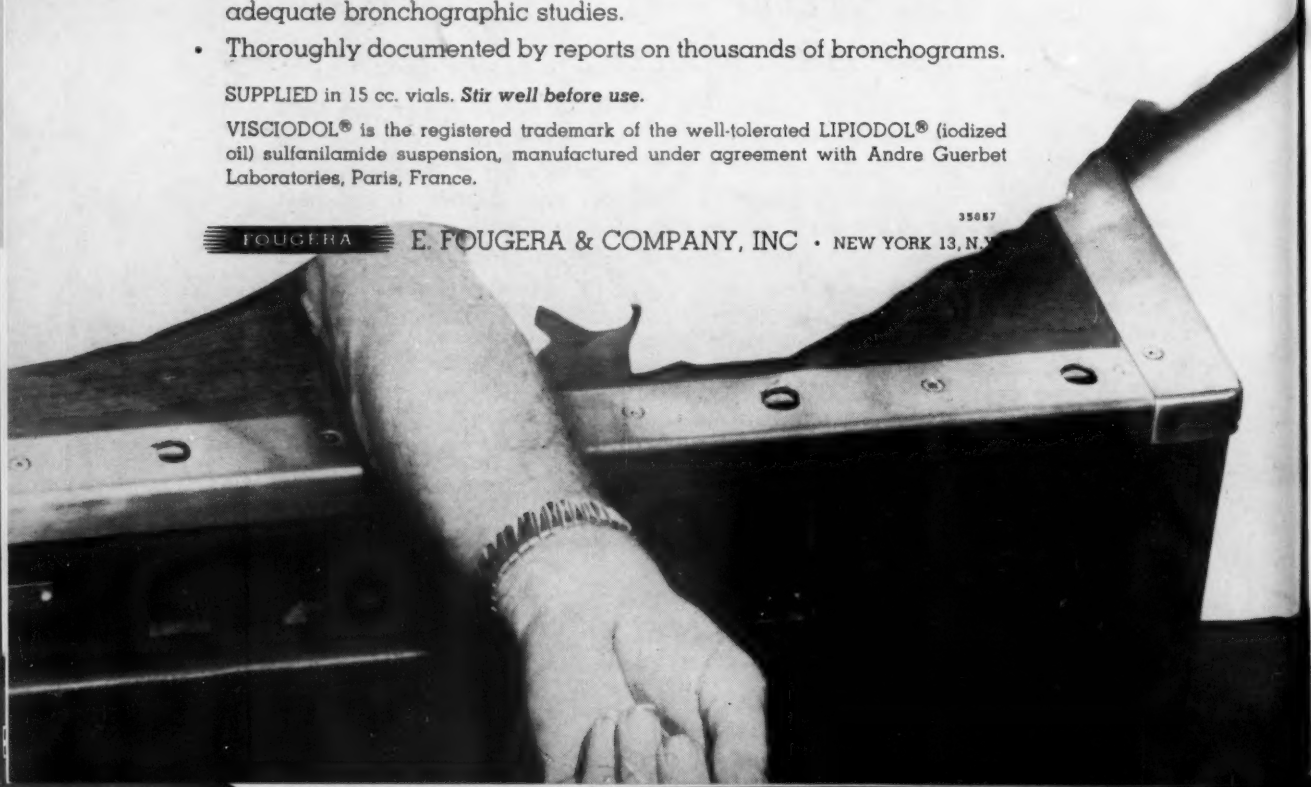

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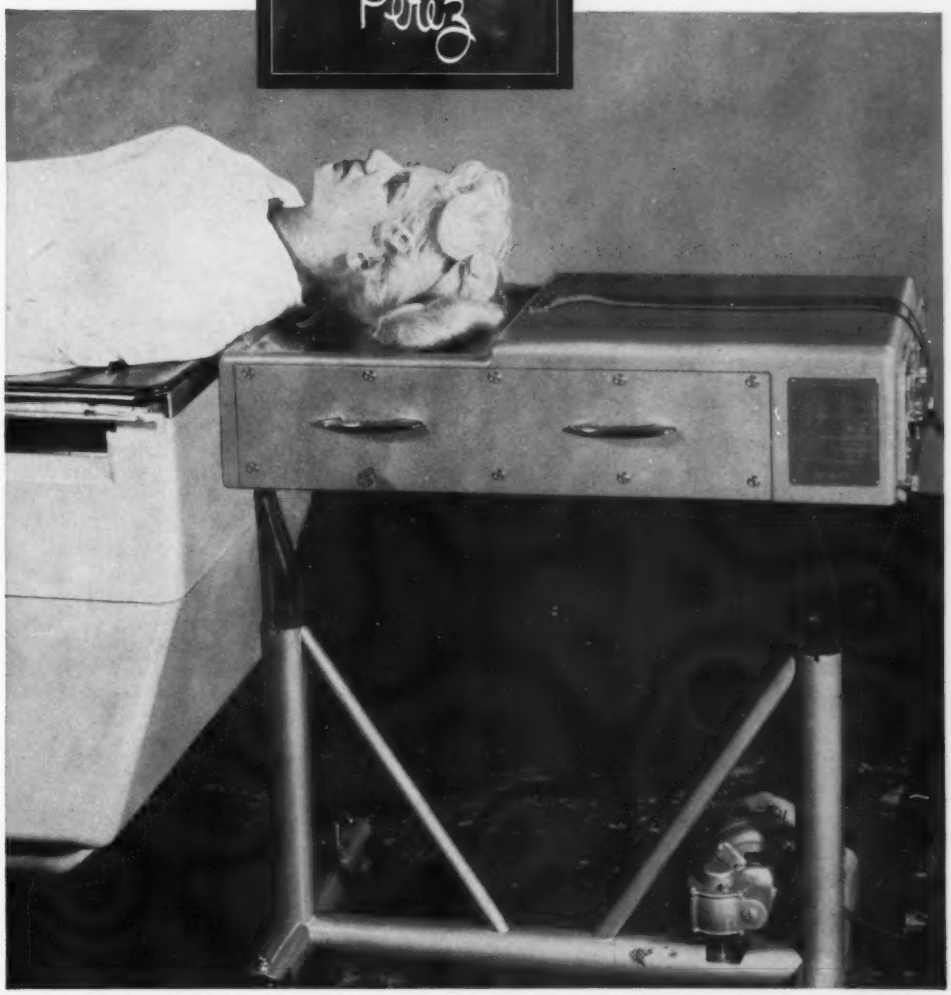

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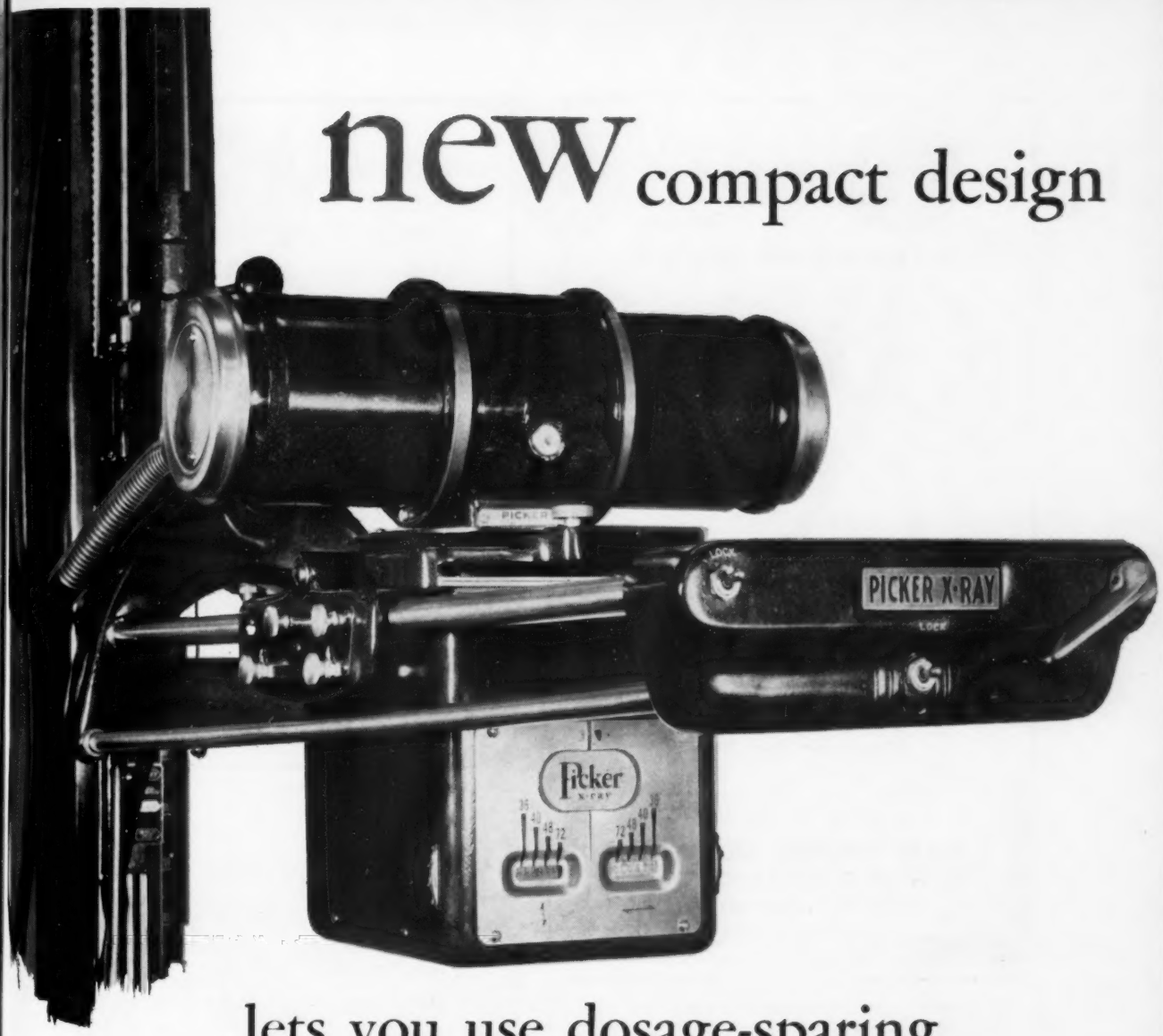

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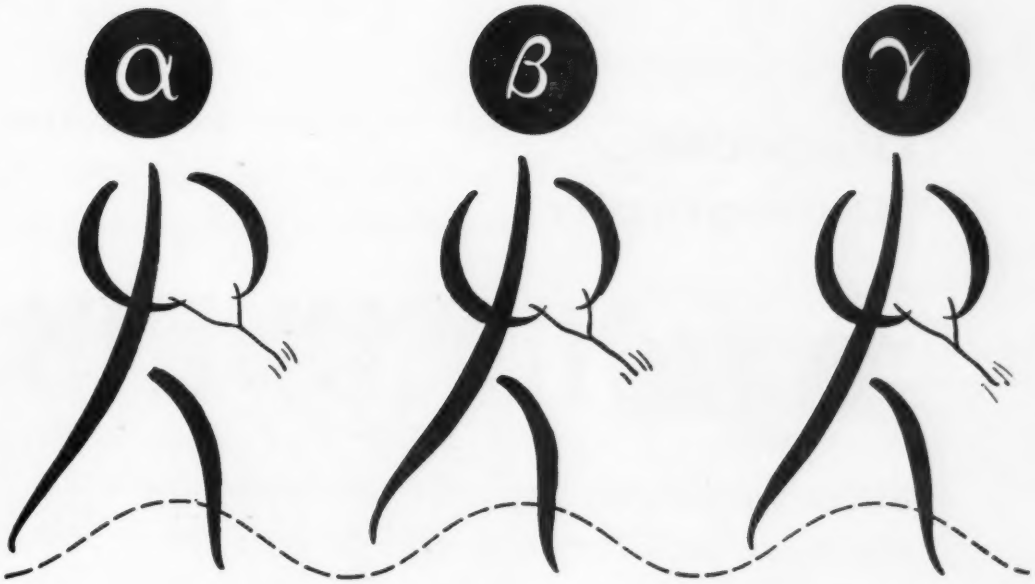

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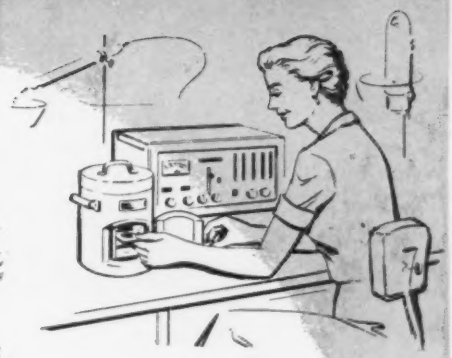

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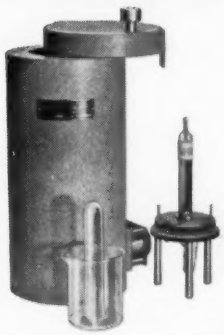
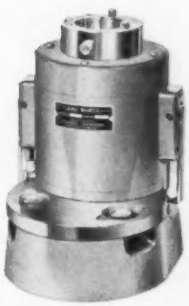


MODEL LS-4

For counting problems concerned with the radioactivity of liquids and pulverized solids, and is especially useful for such medical applications as urinalysis.

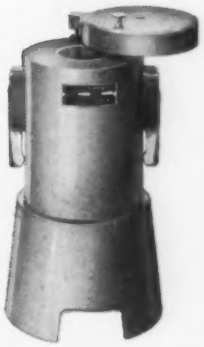
(T/A Bulletin No. 153)



MODEL LS-7M

Multi-purpose shield accepts SD-1 or SD-2 Scintillation Detector, or Geiger tube, and can also be used for proportional counting tubes.

(T/A Bulletin No. 160)



MODEL LS-8

Designed to hold SD-2W Detector equipped with well crystal for measuring low level gamma-emitting samples in liquid or solid form.

(T/A Bulletin No. 148)

For complete details on all Lead Shields, write for Bulletin No. 151.

TECHNICAL ASSOCIATES

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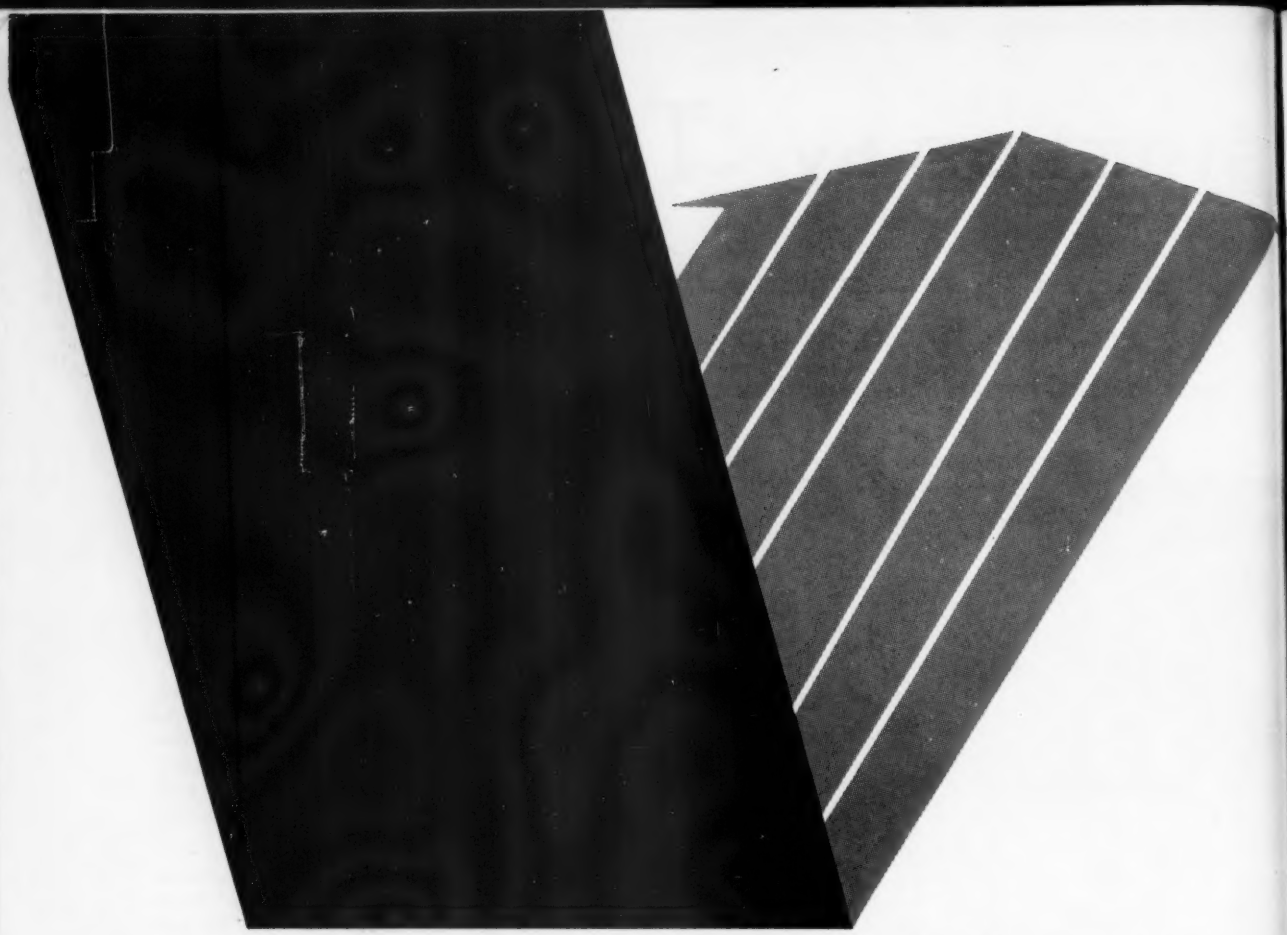

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For complete information write for Bulletin 88

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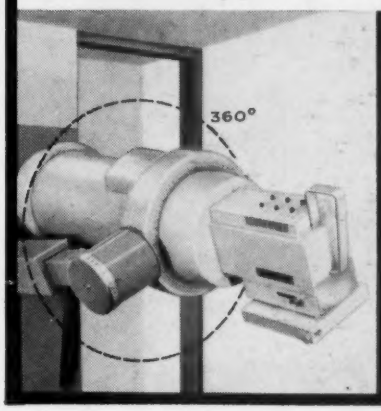
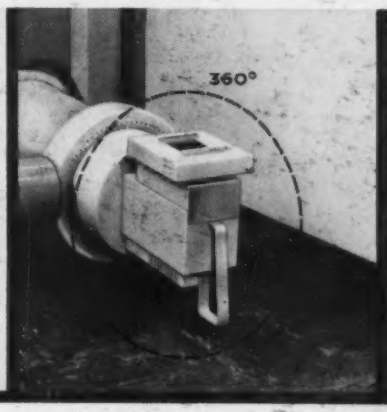
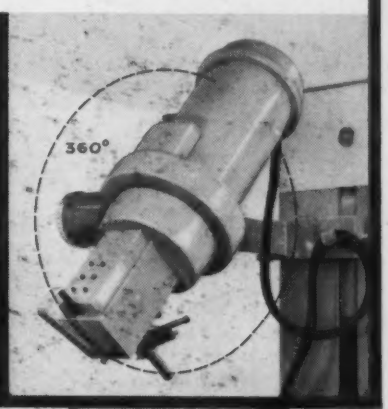
Supporting arm can be swung freely in full circle.



Compact tubehead can rotate fully in gimbal ring.



Tubehead turns on supporting trunnion.



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Want to hear more — about its non-absorbing visual localizer and stabilized electronic power supply? About its beryllium window tube with low inherent filtration? Ask your G-E x-ray representative, or write X-Ray Dept., General Electric Co., Milwaukee 1, Wis., For Pub. A-62.

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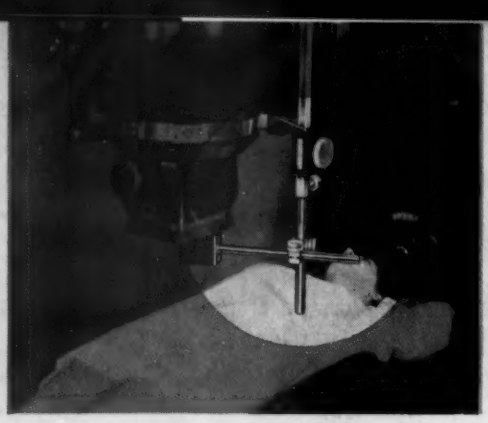
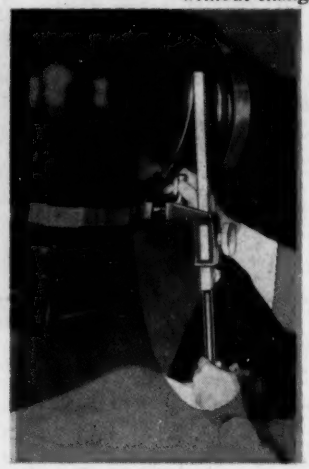
1 The pin-and-arc localizer that accurately establishes beam angulation and position from a known patient-landmark.



2 The adjustable support for beam-shaping blocks that pattern the radiation beam to irregular field profiles.

3 The snap-on open end clear-visi basket cones for applying compression to various field size without changing low skin dose.

4 The back-pointer that sights line of beam traverse, defines point of exit. (There's a pencil-beam *optical backpointer* too, built into the radiation barrier)



5 Measuring and positioning devices are quickly attached or detached from any of four bayonet-lock keyholes spaced at 90° intervals around the sourcehead.

precision positioning devices simplify administration and heighten accuracy of radiation therapy with PICKER Cobalt 60 units

6 The *quick-positioning* Precision Therapy Table that makes it so easy to present the patient at various angulations and levels for fixed-beam technics or to center the tumor to the rotation axis. Pivoting arou a precisely-oriented floor well, it becomes an integral part of the unit, yet is instantly detachable by a pedal release for independent free-wheeling mobility.

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